Pediatrics

VOLUME 2 SEPTEMBER, 1948 NUMBER 3

ORIGINAL ARTICLES

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

I. The Role of Genetic Susceptibility

By MAY G. WILSON, M.D.
New York, N.Y.

CERTAIN individuals are more susceptible than others to many conditions. In recent years it has become clear that in rheumatic fever, susceptibility of the host is an important factor in the pathogenesis of the disease. It was concluded from genetic and epidemiologic studies that susceptibility to rheumatic fever is on a genetic and age basis.[1] Although the susceptible child cannot be identified at the present time, the number of children expected to be susceptible in a group of families of known genotype may be determined on the basis of recessive inheritance. It may, therefore, be postulated that distributed among a group of families of known hereditary background are children who are susceptible and insusceptible to the acquisition of rheumatic fever.

As a direct result of long term observation of rheumatic families over a period of 30 years, a second generation of children of known hereditary background is available to us for exploratory studies. This group includes children from families in which one or both parents are rheumatic, or in which neither parent is rheumatic. In this group there are normal (insusceptible), susceptible and rheumatic children.

The nature of the hereditable factors which may be responsible for susceptibility is obscure. Recent advances in biochemical genetics have provocative implications in rheumatic fever. Of particular interest are the observations which demonstrate that such biochemical reactions as enzyme and protein specificities are gene determined.[2]

As a working hypothesis it seemed reasonable to postulate that in a susceptible child, abnormal physiologic, chemical, immunologic or hormonal responses might be found.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

These studies were aided by a grant from The Commonwealth Fund.
(Received for publication June 8, 1948.)

Differences might then be observed in certain reactions between the normal group and a group containing a high proportion of genetically susceptible children.

This approach does not conflict with the concept that exogenous factors, irrespective of their nature, may also be operative. If the nature of the endogenous factors were known, the role of possible exogenous agents would be clarified.

In order to establish standards for comparison, it frequently has been necessary to make preliminary observations on groups of normal children. These observations not only afford a basis for comparison with susceptibles, but also provide data on possible differences among children of normal families. In some instances, negative observations have provided evidence which tended to exclude certain etiologic concepts in rheumatic fever from further consideration. For example, the possible role of vitamin C in the pathogenesis of rheumatic fever suggested that requirements of ascorbic acid might be found to vary among our children. Studies of the ascorbic acid levels in blood plasma and white blood cells revealed no difference among rheumatic, susceptible and normal children who were on comparable intakes. No evidence was obtained that the requirements for vitamin C during acute rheumatic fever were greater than during other illnesses of comparable severity.[3]

The studies which have been completed on complement titres and electrophoretic patterns represent attempts to evaluate immunologic response and possible differences in serum protein patterns among normal, susceptible and rheumatic children. Other pilot studies are in progress. While it is recognized that the basis for these studies is speculative, the advances in biochemical genetics in recent years offer justification for this approach. It is hoped that some information will be obtained as to the nature of the hereditable factors responsible for susceptibility to rheumatic fever.

References

1. Wilson, May G., Schweitzer, M. D., and Lubschez, Rose, Familial epidemiology of rheumatic fever: genetic and epidemiologic studies, J. Pediat. **22**:468, and 581, 1948.
2. Beadle, G. W., Gene and biochemistry, Currents in Biochemical Research, Interscience Publishers, New York, 1946.
3. Wilson, May G., and Lubschez, Rose, Studies in ascorbic acid with especial reference to white layer; relation of intake to blood levels in normal children and effect of acute and chronic illness. J. Clin. Investigation **25**:428, 1946.

Spanish Abstract

Estudios Inmunologicos y Bioquimicos en Recien Nacidos y Niños con Especial Referencia a la Fiebre Reumática. I. El Papel de la Susceptibilidad Genética

Ciertos individuos son mas susceptibles a muchos estados que otros. En años recientes se ha puesto en claro que en la fiebre reumática, la susceptibilidad del huesped es un factor importante en la patogenia de la enfermedad. Por estudios genéticos y epidemiológicos se concluyó que la susceptibilidad de la fiebre reumática tiene una base en la genética y en la edad.

Como resultado de las observaciones a largo término de familias reumáticas, sobre un periodo de 30 años, hemos podido utilizar para estudios exploratorios una segunda generación de niños de conocidos antecedentes hereditarios. Este grupo incluye niños de familias en que uno de los padres o ambos son reumáticos, o en que ninguno de ellos lo es. En este grupo hay normales (insusceptibles), susceptibles y niños reumáticos.

Como hipótesis de trabajo parece razonable postular que en un niño susceptible pueden encontrarse respuestas de anormalidad fisiológica, quimica, inmunológica u hormonal. Pueden entonces

observarse diferencias en ciertas reacciones entre el grupo normal y el grupo conteniendo una alta proporción de niños geneticamente susceptibles. Esta relación no interfiere con el concepto de que los factores exógenos, independientemente de su naturaleza, pueden tambien ser operativos. Si la naturaleza de los factores endógenos fuera conocida, el papel de los posibles agentes exógenos se aclararia.

Los estudios que han sido completados con titulaciones del complemento y patrones electroforéticos, representan intentos para evaluar respuestas inmunológicas y posibles diferencias en muestras de proteinas séricas entre los niños normales, susceptibles y reumáticos. Otros estudios están en curso. Reconociendose que la base para estos estudios es especulativa, los adelantos en genética bioquimica en los años recientes, justifican estos estudios. Se espera obtener alguna información sobre la naturaleza de los factores hereditarios responsables de la susceptibilidad a la fiebre reumática.

525 E. 68th St.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

II. Complement Titers in Normal Conditions

By PAUL F. DEGARA, M.D., AND HENRY P. GOLDBERG, M.D.
New York, N.Y.

PRELIMINARY to a study of complement in disease,[1] it became necessary to obtain data in normal children of different ages. Previously reported studies in this age group employed methods which do not permit accurate estimation of complement activity.[2-9] Morse[10] suggested the use of 50% hemolysis as an end point, and Brooks,[11] and Wadsworth, Maltaner and Maltaner[12] developed a refined method based on this principle. This method, which gives reproducible results, was used to titrate complement in the blood of newborns[13] and of persons above the age of ten years,[13-15] but to our knowledge values for children of intermediate ages have not been reported. The group of 30 healthy persons ranging in age from 10 to 29 years reported by Pohl and Rutstein[14] had a median complement titer of 0.0049 Ml. The considerably lower values reported by Traub[13] for both newborns and adults may be explained in part by slight changes in the technic of storage and titration used by this author.

MATERIAL AND METHODS

Material

A group of children attending the Pediatric Clinic* was examined at regular intervals and specific inquiry about intervening disease was made at each visit. Only children who were free from all illnesses (including mild upper respiratory infections) for the four weeks preceding the examination were selected for this study.† 1. *Serum:* Blood was obtained under sterile precautions from a cubital vein or, in the younger age group, from the jugular vein, and transferred to a sterile pyrex centrifuge tube. It was kept at room tempertaure for 20 min. and then centrifuged for 20 min. at 2000 r.p.m. The clear supernatant serum was tranferred to a sterile pyrex test tube which was sealed and immediately stored in a box containing solid CO_2 (approximate temperature $-70°C.$) for several weeks.‡

2. *Antisheep Hemolysin:* Commercially available antisheep hemolysin (Lederle) with a minimum unit of 0.1 Ml. of 1:1000 was used.

3. *Sheep Cells:* Sheep's blood was obtained from a slaughter house, filtered, and washed repeatedly with physiologic saline, until the supernatant fluid did not react with con-

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

This study was aided by a grant from The Commonwealth Fund.

(Received for publication June 8, 1948.)

* With few exceptions the children were under continuous medical supervision from birth as part of a genetic study.

† Approximately 40% of this group consisted of children from "susceptible" families.[16]

‡ According to Bier et al,[17] complement preserved in this way does not lose activity even after several months' storage.

centrated nitric acid. Usually four washings were required. A 5% suspension of the cells in physiologic saline was prepared within 48 hours after delivery and used immediately.

4. *Saline:* An 0.85% solution of c.p. sodium chloride in distilled water was freshly prepared for each series of tests.

Methods

1. The "50% hemolysis technic" of Wadsworth et al[12] was used.* Briefly, the procedure was as follows: The serum to be tested was thawed, diluted 1:10 with physiologic saline and distributed into ten tubes so as to contain the following amounts of diluted serum: 0.3; 0.1; 0.09; 0.08; 0.07; 0.06; 0.05; 0.04; 0.03; and 0.02 Ml. The volume in each tube was adjusted to 0.3 Ml. with saline. Two-tenths of a Ml. of the sensitized

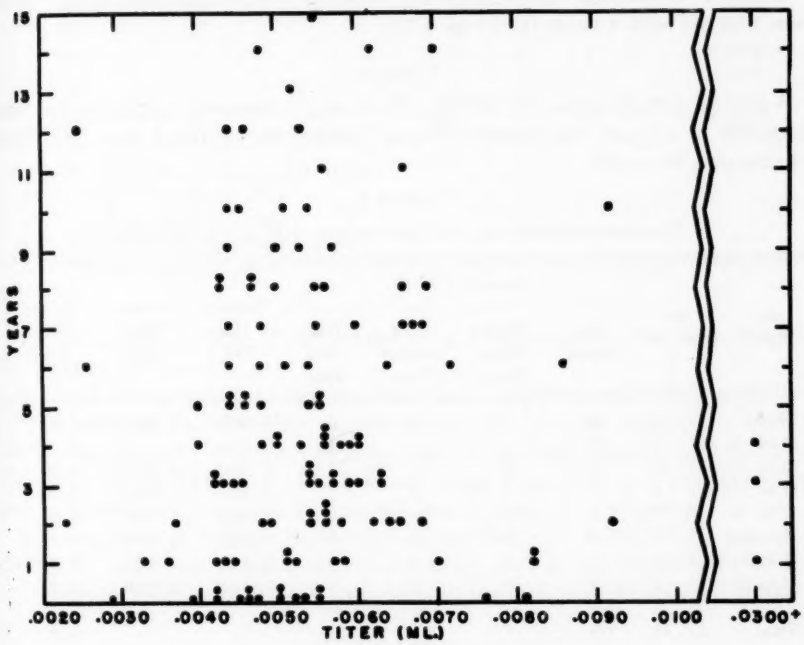


FIG. 1. Complement titer at various ages.

sheep cell suspension (prepared by mixing equal volumes of antisheep hemolysin and washed erythrocytes) were added and the mixtures incubated in a water bath at 37°C. for 15 min.; the racks containing the tubes were shaken by hand every five minutes. The tubes were centrifuged for three minutes at approximately 1000 r.p.m. and the supernates compared with the standard solutions[12] which were freshly prepared for each series of titrations. The values obtained were transferred to graph paper (K & E #359-

* While this study was in progress, a further refinement of the method was described by Mayer, Eaton and Heidelberger[18] and Kent, Bukantz and Rein.[19]

14) and the amount of serum giving 50% hemolysis determined by interpolation from the curve.

It should be noted that the complement activity of a serum (expressed in Ml. required to produce 50% hemolysis) is inversely related to the titer.

2. *Controls.* The following controls were used:

a. 0.005 Ml. of each serum tested, to which was added 0.395 Ml. of saline and 0.1 Ml. of the sheep red cell suspension.

b. 0.3 Ml. of saline added to 0.2 Ml. of sensitized sheep cells.

c. 0.4 Ml. of saline added to 0.1 Ml. of the sheep cell suspension.

Controls *b* and *c* showed no trace of hemolysis in any series of experiments. Twenty-two sera from 19 children showed hemolysis in control *a*, indicating the presence of "natural hemolysins" and therefore were not included in this study.

3. *Error of the Method.* Duplicate determinations on 14 specimens revealed an average error of 1.3% with a range from 0 to 4.2%.

RESULTS

A total of 128 sera from 107 children (52 males, 55 females), ranging in age from three days to 15 years was examined. Figure 1 shows the individual titers, and Table I summarizes the results.

TABLE I

COMPLEMENT TITERS AND AGE DISTRIBUTION OF HEALTHY CHILDREN

Age (yr.)	Sex ♂	Sex ♀	Number of Sera* Examined	With High Titer	With Average Titer	With Low Titer	Highest Titer (Ml.)	Lowest Titer (Ml.)	Mean† Titer (Ml.)
Under 1	9	7	16	2	12	2	0.0029	0.0081	0.0051
1 to 3	17	12	29	4	21	4	0.0023	0.0328	0.0054
3 to 5	12	17	29	0	27	2	0.0040	0.0352	0.0053
5 to 7	11	6	17	1	14	2	0.0026	0.0086	0.0052
7 to 9	7	9	16	0	16	0	0.0043	0.0069	0.0055
9 to 11	1	8	9	0	8	1	0.0042	0.0092	0.0054
11 to 13	4	3	7	1	5	1	0.0025	0.0073	0.0052
13 to 15	2	3	5	0	4	1	0.0048	0.0070	0.0057
Total	63	65	128	8 (6.3%)	107 (83.5%)	13 (10.2%)			0.0053 (±0.00115)‡

* High titer—50% hemolysis with amounts of serum up to 0.0039 Ml.
Average titer—50% hemolysis with amounts of serum from 0.0040 Ml. to 0.0069 Ml.
Low titer—50% hemolysis with amounts of serum of 0.0070 Ml. or more.

† The three sera with complement activity lower than 0.0300 Ml. were not included in the calculation of mean titers.

‡ Standard deviation.

It is apparent from Table I that 83.5% of the values lie between 0.0040 Ml. and 0.0069 Ml. Consequently, titers falling within this range have been classified as "average." Values outside of this range are designated as "high" and "low."

It is also clear from the data in Table I that the complement activity of the children

studied does not vary with age. A similar analysis revealed no difference in the distribution of complement in the two sexes.

The relation of complement titer and season of the year during which blood was obtained is presented in Table II.

TABLE II

RELATION OF COMPLEMENT TITERS OF HEALTHY CHILDREN TO SEASON

Season*	Number of Sera Examined	Number of Sera			Mean† Titer (Ml.)
		With High Titer	With Average Titer	With Low Titer	
Winter	31	1	28	2	0.0053
Spring	17	1	14	2	0.0053
Summer	63	4	50	9	0.0054
Fall	17	2	15	0	0.0052
Total	128	8	107	13	0.0053

* Winter—December, January, and February.
Spring—March, April, and May.
Summer—June, July, and August.
Fall—September, October, and November.

† The three sera with complement activity lower than 0.0300 Ml. were not included in calculation of mean titers.

The data shown in Table II indicate that there is no variation in the mean titer with the season of the year.

Repeated Determinations on the Same Individual: Two blood specimens were obtained from 21 children. In 16 children the paired titers did not differ significantly while in the remaining five the differences exceeded twice the standard deviation of 0.00115 Ml. The time intervals between the two specimens ranged from three to 22 months with an average interval of 12 months. This interval was the same for both groups.

Determinations in Siblings: Children of 30 families were studied. There were three children in each of six families, and two children in each of the remaining 24. In each of 25 families the titers of the siblings differed by less than twice the standard deviation.

COMMENT

The results presented here indicate that complement activity does not vary with age or sex. Over 80% of the children, most of whom were below 10 years of age, had complement titers in the same range as those reported for persons over 10 years[14] and for adults.[15] There was also no apparent relation between complement titer and season of the year in which the specimens were obtained.

The individual complement titer remained constant over prolonged periods in more than one-half of those in whom repeated titrations were performed. This is in agreement with a statement of Dulaney.[15]

The group of 13 healthy children who had a low complement titer is of special interest. They were in apparent good health when blood was withdrawn and, allegedly, had had

no disease during the preceding four-week period. The low complement titers remain unexplained on clinical grounds.

The fact that complement is sensitive to heat may possibly account for an otherwise unexplained low titer. Although special care was taken to avoid overheating the sera in processing the blood, partial inactivation may have occurred in a few instances. Many other factors (pH, abnormal ionic content or strength, exposure to ultraviolet light, etc.) besides heat have been reported as influencing complement activity of human or animal sera. None of these are under suspicion in the sera of low titer of the group studied. The reports of low complement activity in patients with a low plasma vitamin C have not been in complete agreement.[20-22] In any event, the vitamin C intake of the children with low complement activity was as adequate as that of those individuals who showed average or high titers. Recently, Mayer, Osler and Heidelberger[23] emphasized the importance of optimal magnesium content of guinea pig sera in the study of complement activity in this species. In man, however, magnesium is known to undergo only slight variations.[24] It is, therefore, unlikely that a reduction of serum magnesium was responsible for the lower titers observed. The known reduction of complement activity in infectious diseases where antigen-antibody reactions occur will be discussed in a subsequent publication.[1]

SUMMARY

Complement titers of 128 sera from 107 healthy children ranging in age from three days to 15 years are presented. The 50% hemolysis method was used. In 107 instances (83.5%), the complement titer ranged between 0.0040 Ml. and 0.0069 Ml., while eight sera (6.3%) had higher titers, and in 13 instances (10.2%), the complement activity was low. The mean titer for the entire group was 0.0053 ± 0.00115 Ml.

Repeated determinations on the same individuals showed that complement activity usually remained constant over prolonged periods.

Complement activity did not vary with age, sex or season of the year in which the specimens were obtained.

ACKNOWLEDGEMENT

We are pleased to acknowledge our indebtedness to Dr. Michael Heidelberger for his constructive criticisms during the course of this study.

REFERENCES

1. De Gara, P. F., and Goldberg, H. P., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. III. Complement titers in abnormal conditions, Pediatrics **2**:248, 1948.
2. Moro, E., Untersuchungen über die Alexine der Milch und des kindlichen Blutserums, Jahrb. Kinderheilk. **55**:396, 1902.
3. Maugerie, S., Weitere Beitraege zum immunbiologischen Verhalten des Normalserums. VI. Zur Entstehung des Komplements und Normalambozeptors gegen Hammelblutkoerperchen beim Menschen, beim Schwein und bei der Ratte, Zeitschr. Immun. **74**:473, 1932.
4. Pecorella, F., Influenza dell acido nicotinico sul potere complementare del siero di sangue, Boll. Inst. Sieroter, Milan, **19**:282, 1940.
5. Serra, I., Il potere complementare del siero di sangue nei disturbi di nutrizione del lattante, Pediatria **49**:75, 1941.
6. Nattan Larrier, L., Lepine, P., and May, J., Dosage comparatif de l'alexine dans le sang de la mère et dans le sang de l'enfant au moment de la naissance, Compt. rend. Soc. Biol. **97**:671, 1927.

7. Nattan Larrier, L., Grimard, L., and Dufour, J., L'alexine chez le nouveau-né, Compt. rend. Soc. Biol. **125**:358, 1937.
8. Soelling, P., Der Komplementgehalt von Seren von Neugsborenen, Saueglingen und Fruechten, Zeitschr. Immun. **91**:15, 1937.
9. Wasserman, P., and Alberts, E., Complement titer of blood of newborn, Proc. Soc. Exper. Biol. and Med. **45**:563, 1940.
10. Morse, S., Dry permanent standards in Wassermann reaction and technic based on their use, Psych. Bull. N. Y. State Hosp. **9**:47, 1916.
11. Brooks, S. C., Precise titration of complement, J. Med. Res. **41**:399, 1919/1920.
12. Wadsworth, A., Maltaner, E., and Maltaner, F., Quantitative determination of fixation of complement by immune serum and antigen, J. Immunol. **21**:313, 1931.
13. Traub, B., Complement activity of serum of healthy persons, mothers and newborn infants, J. Path, and Bact. **55**:447, 1943.
14. Pohl, A. W., and Rutstein, D. D., Deterioration of complement activity in normal human serum, J. Clin. Investigation **23**:177, 1944.
15. Dulaney, A. D., Complement activity of human serum with especial reference to malaria, Feder. Proc. **6**:425, 1947.
16. Wilson, May G., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever; role of genetic susceptibility, Pediatrics **2**:239, 1948.
17. Bier, O. G., Leyton, G., Mayer, M. M., and Heidelberger, M., Comparison of human and guinea pig complements and their component fractions, J. Exper. Med. **81**:449, 1945.
18. Mayer, M. M., Eaton, B. B., and Heidelberger, M., Spectrophotometric standardization of complement for fixation tests, J. Immunol. **53**:31, 1946.
19. Kent, J. F., Bukantz, S. C., and Rein, C. R., Studies in complement fixation; spectrophotometric titration of complement; construction of graphs for direct determination of 50% hemolytic unit, J. Immunol. **53**:37, 1946.
20. Chu, F., and Chow, B. F., Correlation between vitamin C content and complement titer of human blood plasma, Proc. Soc. Exper. Biol. and Med. **38**:679, 1938.
21. Ecker E. E., Pillemer, L., Griffitts, J. J., and Schwartz, W. P., Complement and ascorbic acid in human scurvy, J.A.M.A. **112**:1449, 1939.
22. Spink, W., Agnew, S., and Mickelsen, O., Ascorbic acid and immunity; relation of ascorbic acid to human complement, J. Immunol. **44**:289, 1942.
23. Mayer, M. M., Osler, A. G., and Heidelberger, M., Quantitative aspects of complement activity, Proc. 112th Meeting, Amer. Chem. Soc., New York, September 15-19, 1947.
24. Greenberg, D. M., Lucia, S. P., Mackey, M. A., and Tufts, E. V., Magnesium content of plasma and red corpuscles in human blood, J. Biol. Chem. **100**:139, 1933.

SPANISH ABSTRACT

Estudios Inmunologicos y Bioquimicos en Recien Nacidos y Niños con Especial Referencia a la Fiebre Reumatica. II. Titulos Del Complemento en Condiciones Normales

El complemento fué titulado por el "Metodo de la hemolisis 50%" en 128 sueros de 107 niños (entre ocho dias y quince años de edad), que estaban normales en el momento de proceder al test y por un periodo ulterior de cuatro semanas. Títulos variando de 0.0040 a 0.0069 Ml. se hallaron en 83.5%, títulos mas altos en 6.3%, y mas bajos en 10.2%. El título medio fué 0.0053 Ml. a 0.00115. No hubo relación entre actividad del complemento y edad, sexo o estación en que la muestra fué obtenida.

525 E. 68th St.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

III. Complement Titers in Abnormal Conditions

By PAUL F. DEGARA, M.D., AND HENRY P. GOLDBERG, M.D.
New York, N.Y.

IN A PREVIOUS study,[1] the range of serum complement of normal, well children was presented. In illness a decrease of complement activity has been reported[2-14] particularly in conditions associated with antigen-antibody reactions, such as serum sickness. Most of the published studies in rheumatic fever do not provide reliable data concerning diagnosis and incidence of changes, and the methods used are now considered inadequate. Furthermore, the results are contradictory. Some [2-8,10-14] observed low complement titers during certain phases of "rheumatic conditions"; others[15,16] were unable to confirm these findings.

TABLE I

COMPLEMENT TITERS OF 155 NORMAL, WELL* CHILDREN IN RELATION TO ANTECEDENT ILLNESS

Interval Between Illness and Test	Persons Examined	Sera Examined	Complement Titers of Sera†					
			High		Average		Low	
			No.	%	No.	%	No.	%
Under 1 month	48	57	8	14.0	44	77.3	5	8.7
Over 1 month	107	128	8	6.3	107	83.5	13	10.2
Over 2 months	86	106	8	7.5	89	84.0	9	8.5
Over 4 months	70	86	7	8.1	70	81.4	9	10.5

* In this and the following tables "well" indicates that patients were well on day of the test.

† Throughout this paper titers are designated "High," "Average" and "Low" according to our previous classification.[1]

The importance of complement in resistance to disease suggested that it might play a role in determining susceptibility to rheumatic fever. This possibility was strengthened by Hyde's observation[17] that a certain stock of guinea pigs, deficient in complement, was more susceptible to disease.

The purpose of this study was to investigate complement activity during rheumatic fever and its role in relation to hereditary susceptibility to this disease.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

This study was aided by a grant from The Commonwealth Fund.

(Received for publication June 8, 1948.)

Material and Methods

A total of 421 sera from 330 children (155 males, 175 females) ranging in age from three days to 15 years was examined over a period of 18 months.*

The following groups were studied:

(1) 29 children with active rheumatic fever (polyarthritis and/or carditis, or chorea);

(2) 71 children with inactive rheumatic fever; and

(3) 230 children from "susceptible" and "insusceptible" families.[18]

The children† were regularly observed during health and intercurrent illness. Upper respiratory infections, such as tonsillitis, pharyngitis, laryngitis, sinusitis and otitis media occurred in 63 children. In addition, there were two patients with pneumonia, eight with meningitis and other pyogenic infections, one with infectious mononucleosis, two with hepatitis, six with glomerulonephritis, two with nephrosis, three with non-specific

TABLE II

Complement Titers of Normal and Rheumatic Children During Health and Disease

Group	Illness	Persons Examined	Sera Examined	Complement Titers of Sera					
				High		Average		Low	
				No.	%	No.	%	No.	%
Normal	None	155	185*	16	8.6	151	81.1	18	10.3
Rheumatic (Inactive)	None	53	70†	9	12.8	58	82.9	3	4.3
Normal	Upper respiratory infections	47	49	4	8.2	31	63.3	14	28.5
	Miscellaneous	28	39	10	25.6	21	54.0	8‡	20.4
Rheumatic (Inactive)	Upper respiratory infections	16	17	3	17.7	14	82.3	0	0
	Miscellaneous	2	2	0	0	2	100.0	0	0
Rheumatic (Active)	Carditis, polyarthritis	21	47	3	6.4	31	65.9	13††	27.7
	Chorea	8	12	0	0	11	91.7	1	8.3

* Mean titer and S.D. 0.0052 ± 0.0012 ml.

† Mean titer and S.D. 0.0052 ± 0.0010 ml.

‡ Obtained from seven patients (four glomerulonephritis, two pyogenic infections, one non-specific arthritis).

†† Obtained from five patients.

arthritis, two with rheumatoid arthritis, two with scarlet fever, one with acute gastroenteritis and one with unexplained hematuria. Whenever possible, blood was obtained from the same patient during health and again during illness. Details of the methods used have been reported in our previous publication.[1]

* A larger number of sera was studied. However, the occurrence of "natural hemolysins" previously noted,[1] was more frequently observed during illness. Sera with "natural hemolysins" were not included in this study.

† Most of the children were under continuous medical supervision from birth as part of a genetic study.

RESULTS

Complement Activity of Normal Well Children in Relation to Antecedent Illness: In our previous study on complement titers of normal well children[1] we excluded all sera from subjects who had been ill within one month because of the possible influence of such illness on complement activity. In Table I the complement titers of children, well at the time of testing but ill within one month, are compared with those of children continuously well for one to four months before testing.

TABLE III

SERIAL* COMPLEMENT TITERS OF NORMAL AND RHEUMATIC CHILDREN DURING HEALTH AND ILLNESS

Group	Illness	Persons Examined	
		Total	Showing Significant Change†
Normal	None	41	8
Rheumatic (inactive)	None	18	3
Normal	Upper respiratory infections	23	9
	Miscellaneous	4	2
Rheumatic (inactive)	Upper respiratory infections	9	3
	Miscellaneous	2	1
Rheumatic (active)	Carditis, polyarthritis	12	7
	Chorea	7	0

* At least one specimen obtained during health and one during illness.

† A decrease during illness greater than twice the standard deviation (0.0012 Ml.).

It is apparent from Table I that complement activity in well children is not significantly affected by an antecedent illness.

Relation of Complement Activity to Susceptibility to Rheumatic Fever: In Table II are presented the data on complement activity of rheumatic children who were well at the time of the test. This group is considered susceptible to rheumatic fever. The distribution of complement titers in this group is not significantly different from normal well children.

Further evidence bearing on the relation of complement to susceptibility to rheumatic fever was obtained by first determining complement activity of six children in whom both parents were rheumatic. The titers were found to be within normal range. In addition, the titers of children from families "susceptible" to the acquisition of rheumatic fever[18] were compared with those from families "insusceptible" to this disease. There were 28 siblings from 12 "susceptible" families and 38 siblings from 18 "insusceptible" families. The distribution of complement titers was not significantly different in the two groups.

TABLE IV

Complement Titers of Children with Active Rheumatic Fever

Patient No.	Age	Laboratory No.	Antecedent Illness	Major Manifestation	Duration Active Rheumatic Fever	Clinical and Laboratory Data*	Titers	
							This Specimen	In Health
1	10	194	None	Polyarthritis	<1 week	F; ESR; WBC	0.0048	0.0047
2	10	600 621 641 663	Sore throat	Polyarthritis	3-4 weeks 1–2 months 1–2 months 2–3 months	R; ESR R.; ESR J.P.; J.S. R.; J.P.; J.S.	0.0062 0.0057 0.0044 0.0042	0.0036
3	11	469	Upper respiratory infection	Polyarthritis	3–4 weeks	ESR	0.0062	0.0046
4	7	684	Upper respiratory infection	Polyarthritis	2–3 weeks	ESR	0.0055	
5	10	629 635	Tonsillitis	Polyarthritis	1–2 weeks 2–3 weeks	ESR ESR	0.0055 0.0055	
6	10	596 598 615 623 644 656 665	None	Polyarthritis	1–2 weeks 1–2 weeks 3–4 weeks 1–2 months 1–2 months 1–2 months 2–3 months	ESR ESR F; J.P.; ESR ESR ESR ESR ESR	0.0036 0.0042 0.0030 0.0053 0.0041 0.0044 0.0055	
7	14	571	None	Polyarthritis	1 week	F	0.0043	0.0057
8	10	185	None	Polyarthritis	<1 week	F; ESR	0.0072	0.0040
9	12	622 633 643 655	Sore throat	Polyarthritis	<1 week 2–3 weeks 3–4 weeks 1–2 months	F; WBC; ESR J.P.; ESR J.P.; ESR J.S; ESR	0.0225 0.0300 0.0300 0.0090	0.0065
10	11	692 694 695	Upper respiratory infection	Polyarthritis	<1 week 1–2 weeks 1–2 weeks	J.P.; F; ESR; V.C. ESR; V.C. ESR	0.0050 0.0064 0.0066	
11	9	687	Pharyngitis	Polyarthritis	2–3 weeks	ESR; F; V.C.	0.0030	
12	6	710	Sore throat	Polyarthritis	1–2 weeks	N.	0.0064	
13	8	713	Pharyngitis	Polyarthritis	5 days	J.P.; J.S.	0.0040	
14	9	276	Tonsillitis	Active carditis	2–3 months	N.; ESR; V.C.	0.0047	0.0051
15	15	223	Sore throat	Active carditis	1–2 months	J.S.	0.0057	0.0055
16	10	241 266	None	Active carditis	2–3 months 3–4 months	N. F; ESR; N.	0.0046 0.0064	0.0033
17	10	297	Sore throat	Active carditis	1–2 weeks	V.C.	0.0068	0.0052
18	11	538 595 605 626 634	None	Active carditis	3–4 weeks 2–3 months 2–3 months 3–4 months 3–4 months	F; V.C.; C.F. N. N. V.C.; C.F. V.C.; ESR	0.0040 0.0048 0.0066 0.0049 0.0057	0.0052
19†	10	650 651	Unknown	Active carditis	years years+4 days	C.F. C.F.	0.0094 0.0098	
20†	9	358 359 368 413 441	Tonsillitis	Active carditis	2–3 months 2–3 months 3–4 months 4–5 months 5–6 months	C.F. C.F. C.F. C.F. C.F.	0.0074 0.0073 0.0066 0.0300 0.0125	
21†	9	691 697	None	Active carditis	7 months 7 months	C.F. C.F.	0.0070 0.0073	
22	7	225	None	Chorea	1–2 weeks		0.0043	0.0051
23	9	202	Upper respiratory infection	Chorea	1–2 months		0.0047	0.0056
24	15	630	None	Chorea	<1 week		0.0040	0.0044
25	9	584 606	None	Chorea	2 weeks 1–2 months		0.0060 0.0053	0.0053
26	11	346	None	Chorea	2–3 months		0.0079	0.0064
27	8	255	None	Chorea	3 months		0.0052	0.0058
28	8	614 624	None	Chorea	1–2 months 1–2 months		0.0062 0.0059	
29	12 13	243 379 400	None	Chorea	3–4 weeks 6–7 months 7–8 months		0.0050 0.0054 0.0053	0.0057

* F: Fever
ESR: Elevated sedimentation rate
WBC: Leukocytosis
R.: Rash
J.P.: Joint pains
J.S.: Joint swelling
N.: Nodules
V.C.: Diminished vital capacity
C.F.: Congestive failure
†Died within ten days of last specimen.

From the data in Table II it is also apparent that low complement titers were observed in 20.4 to 28.5% of sera from normal children during illness but in only 10.3% during health. While this difference is statistically significant, it should be noted that complement activity was within normal limits in the majority of the patients during illness. However, a small group of rheumatic subjects showed no low titers during intercurrent upper respiratory infections.

Serial determinations during health and illness are presented in Table III. The changes in complement titers of normal and of rheumatic subjects during intercurrent illness were comparable.

Complement Titers in Active Rheumatic Fever. The data on patients with active rheumatic fever are given in Tables II, III and IV.

A comparison of the titers during active and inactive rheumatic fever (Table II) reveals significant increase in the number of low titers in patients with polyarthritis and carditis. Again it is apparent that the majority of the patients had normal complement activity. One of the eight patients with chorea had a low complement titer. Serial studies (Table III) were in agreement with these observations.

In Table IV it may be seen that in accordance with the findings on normal children, antecedent illness apparently did not influence the complement activity of patients with active rheumatic fever. Excluding the group with chorea, blood was first obtained during the first week of illness from six patients; two of them had a low titer.

An analysis of the titers of patients receiving oral salicylate medication, not exceeding 3 gm./day, revealed no influence on the complement activity.

COMMENT

Low complement titers may be considered the result of deficient production, abnormal excretion or increased inactivation of complement. Interference with production has been noted in certain hepatic conditions, and abnormal excretion may explain loss of complement in kidney disease. However, the most frequent cause for low complement activity is its increased inactivation in the course of antigen-antibody reactions in vivo. Reports of complement activity in various diseases[2-16, 19] reveal that it may vary during the course of illness and with the severity of the condition. It is noteworthy that Rutstein and Walker[14] found a low complement titer in only one-half of 16 patients suffering from a typical antigen-antibody reaction; namely, serum sickness.

Complement activity apparently returns to normal fairly rapidly since this study reveals that antecedent illness did not influence the titer. During intercurrent illness approximately one out of four sera studied had a low titer. Abnormal excretion during nephritis may have been responsible for decreased complement activity in five instances. The two children with liver disease and jaundice had normal complement titers. Thus the decrease of complement activity in the remainder probably reflects the occurrence of an antigen-antibody reaction. Although the majority of the patients had normal titers, it is possible that some of them had infections which were not severe enough to elicit such a reaction. In other instances the timing of the test may not have been optimal.

The small group of rheumatic subjects examined during intercurrent illness had no low complement titers. This observation is not considered significant since the results of serial determinations were comparable to those in non-rheumatic subjects.

The majority of the patients with active rheumatic fever had complement titers within

normal limits. Low titers were noted in six of 29 patients. Three of four children with congestive failure had a low complement titer which may have been in part the result of impaired production .Whether the decrease of complement activity in the few patients with active rheumatic fever reflects an antigen-antibody reaction cannot be determined from our limited data.

Our results provide no evidence for any relation between complement and susceptibility to rheumatic fever. The range of values for complement activity of patients known to be susceptible to the acquisition of rheumatic fever did not differ from that of insusceptible children when examined in health and during illness.

Summary

Complement activity of 421 sera from 330 children was determined.

Complement activity was not influenced by antecedent illness.

Low complement titers were found in approximately 25% of 75 normal children during intercurrent illness.

Approximately 25% of 29 patients with active rheumatic fever had low complement titers.

No evidence was obtained to indicate that complement activity is a factor in hereditary susceptibility to rheumatic fever.

Acknowledgement

We are pleased to acknowledge our indebtedness to Dr. Michael Heidelberger for his constructive criticisms during the course of this study.

References

1. deGara, P. F., and Goldberg, H. P., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. II. Complement titers under normal conditions, Pediatrics **2**:242, 1948.
2. Cadham, F. T., Complement in health and disease, Canad. Med. Assoc. J. **16**:352, 1926.
3. Hadjopoulos, L. G., and Burbank, R., Role of complement in health and disease; clinical study of hemolytic complement of human sera, J. Lab. & Clin. Med. **14**:131, 1929.
4. Veil, W. H., and Buchholz, B., Der komplementschwund im Blute. Eine bedeutsame immunbiologische Reaktion beim rheumatischen Infekt und ihre Beziehung zur allgemeinen Pathologie des Rheumatismus, Klin. Wchnschr. **11**:2019, 1932.
5. Buchholz, B., Die Bedeutung der Komplementveraenderung bei der rheumatischen Infektion, Med. Welt **7**:1775, 1933.
6. Schnable, P., Komplementuntersuchungen bei rheumatischen Erkrankungen, Med. Klin. **29**:714, 1933.
7. Coburn, A. F., Observations on mechanism of rheumatic fever, Lancet **2**:1025, 1936.
8. Horster, H., and Loris, E., Ueber die Bedeutung der Komplementbestimmung im Blute bei Rheumatismus und Nephritis fuer die Pathogenese, Prophylaxe, Prognose und Differential diagnose, Muenchen. med. Wchnschr. **83**:473, 1936.
9. Kellett, C. E., Complement titers in acute nephritis, with special reference to causation by reversed anaphylaxis, Lancet **2**:1262, 1936.
10. Meersseman, F., and Perrot, H., Le pouvoir alexique des serums humains a l'etat normal et pathologique, Compt. rend. Soc. de biol. **124**:770, 1937.
11. Scartozzi, C., Del potere complementare; ie potere complementare nei vari stati fisiologici e patologici dell'uomo, Gior. di batteriol. e immunol. **19**:797, 1937.
12. Rachmilewitz, M., and Silverstein, W., Amount of complement in blood in rheumatic fever and rheumatoid arthritis, J. Lab. & Clin. Med. **22**:1240, 1937.

13. Ecker, E., Seifter, S., Dozois, T. F., and Barr, L., Complement in infectious disease in man, J. Clin. Investigation **25**:800, 1946.
14. Rutstein, D. D., and Walker, W. H., Complement activity in pneumonia, J. Clin. Investigation **21**:347, 1942.
15. Netousek, M., and Pesek, J., Dosage de l'alexine dans le serum humain, Soc. Franc. de Hematol. Presse Med. **43**:1303, 1935.
16. Schuchardt, E., Beitrag zum Komplementgehalt im menschlichen Serum, Ztschr. f. Immunitatsforsch. u. exper. Therap. **97**:1, 1939/40.
17. Hyde, R. R., Complement deficient guinea-pig: study of an inheritable factor in immunity, Am. J. Hyg. **15**:824, 1932.
18. Wilson, May G., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. I. The role of genetic susceptibility, Pediatrics **2**:239, 1948.
19. Seifter, S., and Ecker, E. E., Complement and isohemagglutinins in urinary proteins, J. Clin. Investigation **25**:809, 1947.

SPANISH ABSTRACT

Estudios Numerologicos y Bioquimicos en Infantes y Ninos, con Referencia Especial a la Fiebre Reumatica. III. Titrelos del Complemento en Condiciones Anormales

El complemento fue titrelado por el "método de hemolisis 50%." La actividad del complemento no fue influenciada por antecedentes patologicos. Se encontraron titrelos bajo del complemento en aproximadamente el 25% de 75 niños normales que estuvieron enfermos cuando se efectuó el test. Aproximadamente 25% de 29 pacientes con fiebre reumatica activa tenían titrelos bajo de complemento.

No se observaron datos que indicaron que la actividad del complemento fue un factor en la susceptibilidad hereditaria de la fiebre reumatica.

525 East 68th St.

INFECTIOUS CROUP: I. ETIOLOGY

By EDWARD F. RABE, M.D.
New Haven, Conn.

THIS report is based on a study of 347 cases of infectious croup admitted to the pediatric service of the New Haven Hospital, during the past ten years (1937-1946 inclusive). The study is prompted by the fact that there is considerable difference of opinion as to the etiologic role of the various bacteria found in association with this disease. For the purposes of this study infectious croup is defined as a disease of the upper respiratory tract characterized by inflammation of the rhinopharynx and downward spread of the infection leading to variable degrees of stenosis of the laryngeal, laryngotracheal, or laryngotracheobronchial air passages. This stenosis is due to edema and is aggravated by membrane formation.

MATERIAL AND METHODS

The Grace-New Haven Community Hospital, New Haven Unit, is a general hospital in a community of over 200,000 people. The pediatric service is composed of 68 beds, half of them being in the isolation pavilion. To this unit are admitted all patients whose illness is considered infectious. To the other unit are admitted all medical pediatric non-infectious cases. From this latter unit data were derived to serve as control for the infectious unit studies. The upper age limit of this service is the sixteenth birthday. Yearly admissions to the service during the period 1937 through 1946 averaged 1,006 patients, the lowest being 733 in 1937 and the highest, 1,204, in 1943.

Bacteriology: At the time of admission to the hospital all patients have cultures taken of material from the nose, throat, blood and any purulent lesion. This material is plated on agar media in whose preparation extensive use of rabbit's blood is made. The blood agar plates are incubated at 37.5° C. and are read when bacterial growth seems optimal, usually after 18 to 24 hours' incubation. Nasal swab material is routinely incubated in 1.0 cc. of blood broth. From this tube suitable organisms can be identified by capsular swelling a few hours after initial inoculation of the media. Blood cultures are made by incubating 5.0 cc. of patient's blood in 50.0 cc. of broth, and by mixing 2.0 cc. of patient's citrated blood with 15.0 cc. of infusion agar to form a pour plate. The broth culture and pour plate are incubated at 37.5° C. aerobically and are read as negative if a smear of the broth after five days of incubation shows no organisms, and if no colonies are visible in the pour plate at the end of 48 hours of incubation. In H. influenzae type B bacteremia visible colony formation is frequently not obtained in the pour plate. However, when a loopful of this medium, previously incubated for 24 hours, is transferred to blood broth, abundant growth occurs. Cultures of material from the larynx, trachea, or bronchi obtained at endoscopy were made on blood agar plates and "rapid typing broth" (1.0 cc. of blood broth).[1]

Identification of bacteria was made on the basis of colonial appearance, stained smear, and serologic reaction in the instance of H. influenzae type B, pneumococci and meningococci. Hemolytic str. were serologically grouped by the method of Lancefield and typed by Griffith's slide agglutination technic.[2] Virulent diphtheria organisms were identified by guinea pig inoculation. When staphylococci were recovered from a purulent lesion or from the blood, pathogenicity was frequently determined by their ability to ferment mannite and to coagulate plasma.

Repeated cultures were made during the course of the illness as seemed indicated. If a patient died, immediate postmortem heart's blood and spinal fluid cultures were made.*

From the Department of Pediatrics, Yale University School of Medicine, and the University Service, Grace-New Haven Community Hospital.

(Received for publication April 1, 1948.)

* All bacteriologic procedures were done by Mrs. Mildred D. Fousek, bacteriologist for the pediatric service for 12 years.

Classification of Cases: The patients in this series were divided into three groups on the basis of the clinical or endoscopic evidence of downward progression of the disease. Thus cases with signs of upper respiratory tract obstruction (inspiratory and/or expiratory stridor, supraclavicular, intercostal and subcostal retraction) and a hoarse voice with brassy cough were classified as laryngitis. Cases with the above symptoms plus loud, moist rales or rhonchi apparently originating in the trachea or bronchi were classified as laryngotracheitis. Cases with a combination of the above symptoms plus patchy areas of fine bubbling or sibilant rales were classified as laryngotracheopneumonitis although strictly speaking they should be called laryngotracheobronchopneumonitis, indicating that the pathologic process had extended into the bronchi, bronchioles, and groups of alveoli. Table I

TABLE I

COMPARISON OF CLINICAL TYPES OF INFECTIOUS CROUP*

Type	Duration of Hospitalization (Surviving Patients)	Mortality (%)	Cases
Laryngitis	7.3 days	1.1	175
Laryngotracheitis	10.8 days	2.8	107
Laryngotracheo-pneumonitis	17.7 days	18.6	43

* Patients with diphtheria (22 cases) are not included since the duration of hospitalization was influenced by such additional factors as myocarditis and persistence of positive rhinopharyngeal cultures.

supports this classification since it shows that the duration of hospitalization and mortality increase as the infection spreads.

It was felt that the three clinical types probably represented variations of the same infectious process. However, each type was analyzed separately to discover if a particular bacterial agent might be recovered in a high percentage of the more serious forms of the disease.

RHINOPHARYNGEAL FLORA IN DISEASES OF THE RESPIRATORY TRACT

The first report of croup due to an organism other than C. diphtheriae was by MacNab in 1915.[3] A tracheal membrane culture yielded a "pure streptococcus." Since this time numerous organisms have been given an etiologic role, but the hemolytic str. has been the most frequently named (Neffson).[4]

Difficulty in interpreting the bacteriologic findings in infectious croup has stemmed from the lack of recognition of what constitutes the normal flora of the upper respiratory tract in children. In Table II, column 1 results of routine cultures of the rhinopharynx in 1,356 pediatric patients with non-infectious diseases are shown. These cultures were taken during the years 1937-1944 inclusive. (Cultures of children with rheumatic fever, chorea, and nephritis were omitted because of the close association between hemolytic streptococcal upper respiratory infections and these diseases.)

Attention is called to the fact that the average carrier rate of beta hemolytic str. was 10%. Thirty-four percent of the children carried various types of pneumococci. H. influenzae, either untyped or not type B, were recovered from the rhinopharynx of 33% of this group. (H. influenzae organisms were routinely typed during the last four years of the survey.) Staphylococci and green streptococci were recovered from the rhinopharynx of 99 and 92% respectively.

Because of the very frequent occurrence of green streptococci and staphylococci in the rhinopharynx of normal children these organisms are considered as part of the

normal rhinopharyngeal flora. It is conceivable, as has been reported by Neffson and Williams,[4, 5] that the staphylococcus may sometimes be an etiologic agent in producing infectious croup. However, judging from our own experience and a critical appraisal of the literature, staphylococcal croup must be a condition of great rarity. H. influenzae, hemolytic str., and pneumococci are regarded as potential pathogens because of their comparatively infrequent occurrence in the rhinopharynx of normal individuals, and their high incidence in the rhinopharynx of individuals sick with a disease in which one of these organisms is the known etiologic agent.

In order to study the simultaneous occurrence of more than one potential pathogen in the rhinopharynx, diseases in which these bacteria are the known etiologic agent

TABLE II

RESULTS OF RHINOPHARYNGEAL CULTURES IN THREE CONTROL GROUPS OF PATIENTS

(Percent of Positive Cultures Obtained)

Organism	Normal Patients (1356 Cases)	Pneumococcal Pneumonia (302 Cases)	Scarlet Fever (86 Cases)
H. influenzae*	32.8%	55.8%	41.8%
H. str.	10.0%	6.3%	96.0%
Pneumococci	33.8%	100.0%	31.0%
Green streptococci†	92.0%	94.8%	98.8%
Staphylococci	99.1%	100.0%	100.0%

* Untyped or not type B.

† This term is used because some green pigment-producing streptococci are serologically hemolytic str., and some organisms which are biochemically Str. viridans do not produce green pigment.

were selected. Table II, column 2 shows the rhinopharyngeal flora encountered in children with pneumococcal pneumonia during three years of observation. The diagnosis was made on the basis of history, physical examination, high leukocyte count, positive X-ray findings in the chest, and clinical course, as well as positive blood cultures in some cases. Only those cases were included which grew positive rhinopharyngeal cultures for the pneumococcus. It is to be noted that 56% of these 302 children had H. influenzae in the rhinopharynx (not type B in two years of the study when they were routinely typed) and 7% harbored beta hemolytic str. Green streptococci and staphylococci were recovered in 95% and 100% of the cases respectively.

In a review of one year's statistics on scarlet fever when a total of 86 cases with rash was seen, 96% of the patients had positive rhinopharyngeal cultures for beta hemolytic str. (Table II, column 3). Thirty-one percent of this group harbored pneumococci in the rhinopharynx and 42% H. influenzae. Staphylococci were recovered from the rhinopharynx of all of these patients, and green streptococci were recovered from all but one patient.

It thus becomes evident that the mere presence of a potential pathogen in the rhinopharyngeal cultures of patients with a respiratory tract infection does not necessarily mean that the organism is the cause of the disease. Instead, the organism must be recovered from a high percentage of a series of cases and the significance of the

organism must be interpreted in the light of the patient's clinical course and in conjunction with appropriate laboratory procedures. Consistently similar clinical, bacteriologic and pathologic findings in a large series of cases help to establish the position of the organism as an etiologic agent.

In the present study of infectious croup the cases were initially grouped according to the clinical signs, symptoms, and course of the disease and the bacteriology of the rhinopharynx and blood. Subsequent review of the living and morbid pathology of the cases in these groups revealed a consistent and specific picture for each group. Thus on the basis of a correlation among clinical, bacteriologic and pathologic findings we have divided infectious croup into three distinct etiologic categories; namely, diphtheritic croup, H. influenzae type B croup, and so-called "virus" croup.*

TABLE III

SUMMARY OF BACTERIOLOGIC FINDINGS IN THE THREE ETIOLOGIC TYPES OF INFECTIOUS GROUP

(Percent of Positive Cultures Obtained)

Rhinopharyngeal Cultures	Diphtheritic Croup (22 Cases)	H. influenzae Type B Croup (28 Cases)	"Virus" Croup (297 Cases)
H. influenzae	9.0%*	96.4%†	42.2%‡
H. str.	23.0%	4.0%	8.8%
Pneumococci	45.0%	39.0%	52.2%
C. diphtheriae (virulent)	100.0%	—	—
	Blood Cultures		
H. influenzae	—	89.2%‡‡	—
H. str.	—	—	—
Pneumococci	13.6%	—	0.4%
C. diphtheriae (virulent)	18.2%	—	—

* Untyped or when typed not type B.

† From 82.2% (23) of the cases type B organisms were cultured, the remaining 14.2% (4 cases) carried untyped H. influenzae. Of the 17.8% (5 cases) without type B organisms in the rhinopharynx, all had H. influenzae type B bacteremia.

‡ 0.67% of cases positive for type B. However, clinical course and pathology indicated organism was not responsible for the disease. Remaining cases untyped or when typed not type B.

‡‡ All type B.

Bacteriology of Infectious Croup: The clinical picture, pathology and course of croup due to H. influenzae type B and of so-called "virus" croup are different from each other and from croup due to C. diphtheriae. These differences will be discussed in subsequent publications.[6, 7] Inasmuch as the clinical course and pathology of these three types of croup are individually consistent, a single etiologic agent would seem likely for each type of croup.

* This term has been chosen in deference to the present trend of opinion concerning the etiology of the disease. An alternate term is "non-bacterial croup."

In the 22 cases of croup due to C. diphtheriae the causative organism was recovered from the rhinopharynx in every case (100%). No antemortem blood cultures were positive, but four of the five deaths in this series had postmortem heart's blood cultures positive for C. diphtheriae. Of these four cases, three had, in addition, a pneumococcal bacteremia, Type XIV in two instances, and Type IX in the third. Rhinopharyngeal cultures yielded pneumococci in 45% of the cases, beta hemolytic str. in 23% of the cases and H. influenzae in 9% of the cases. These results are summarized in column 1 of Table III.

There were 28 cases of croup due to H. influenzae type B (Sinclair[8]) in the series. Rhinopharyngeal cultures yielded H. influenzae in 96% of the cases, 82% of these being type B, the remaining 14% being untyped.* However, 89% of the blood cultures

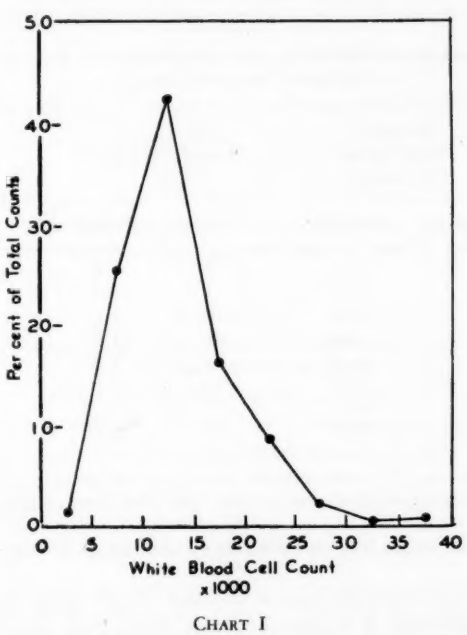


CHART I

were positive for H. influenzae type B, the three negative blood cultures occurring in clinically bacteremic cases with H. influenzae type B in the nose. In addition 39% of the rhinopharyngeal cultures were positive for pneumococci of various types and 4% were positive for beta hemolytic str. (Table III, column 2).

The symptom complex presented by the remaining 297 cases of infectious croup was so consistent that a common etiologic agent would seem likely. Table III, column

* In every instance of blood cultures positive for H. influenzae typing was done. This was not true for nose and throat cultures prior to 1941 and this accounts for the finding of H. influenzae, not typed, in the earlier years of this study.

3 shows a tabulation of the rhinopharyngeal cultures of these 297 cases. Most striking is the fact that no one potential bacterial pathogen occurs in consistently high incidence. Although no virus studies were done on these patients the following collateral evidence is presented to show why it is believed that some non-bacterial agent or agents initiate the disease under discussion.

The incidence of H. influenzae in so-called "virus" croup is somewhat higher than in the "normal" group (Table II, column 1), but this is predictably so because the incidence of pneumococci is also higher (Yang).[9] However, the incidence of H. influenzae is only 42%, and this is in definite contrast to the incidence of H. influenzae in croup due to type B of this organism. It is noteworthy that the over-all incidence of hemolytic str. in this group of cases is lower than that of the normal carrier rate. This is remarkable when we consider that the incidence of obvious forms of streptococcal disease is high in this community and makes up 15% of all admissions to our clinic.

TABLE IV

COMPARISON OF TYPES OF PNEUMOCOCCI OCCURRING IN RHINOPHARYNX OF THREE GROUPS OF PATIENTS

Pneumococcus Type	So-called "Virus" Croup (147 Cases)*		Normal (101 Cases)†		Pneumococcal Pneumonia (142 Cases)†	
	Number	Percent	Number	Percent	Number	Percent
I, III	10	6.8	7	6.9	42	29.6
V	—	—	1	1.0	20	14.1
VI	23	15.6	9	8.9	9	6.3
XIV	5	3.4	14	13.9	18	12.7
XIX	21	14.3	6	5.9	8	5.6
XXIII	15	10.2	4	4.0	12	8.4
Total	74	50.3	41	40.6	109	76.7

* This includes cases from 1937–1944, inclusive, years in which routine typing of pneumococci was possible. Such typing was impossible during the years 1945–1946 due to limited availability of typing serum.

† Normal patients and patients with pneumonia were studied during the same year, 1939.

The higher incidence of pneumococci in so-called "virus" croup than in the "normals" is not to be overemphasized. If pneumococci were etiologically important, a significantly elevated white blood cell count would be expected in a high percentage of cases. Chart I illustrates that this is not true with respect to so-called "virus" croup. The serologic type of the pneumococci was also taken into consideration in the analysis of rhinopharyngeal cultures since it is recognized that some types, notably the so-called low-numbered types and Type XIV, are important pathogens in that they are frequent causes of pneumococcal pneumonia. Table IV shows that pneumococcal types frequently responsible for pneumococcal pneumonia in children are infrequently recovered from patients with so-called "virus" croup. Furthermore, pneumococci were recovered in 45% of the cases of diphtheritic croup and 39% of the cases of croup due to H. influenzae type B. The differences between these incidences of rhinopharyngeal pneumo-

cocci and the incidence of rhinopharyngeal pneumococci in so-called "virus" croup (52%) are not statistically significant (Chi-square test). Finally, in a disease in which pneumococci are accepted as the etiologic agent, i.e., lobar pneumonia, these bacteria have been recovered in 96% of the cases (Heffron).[10]

When so-called "virus" croup is considered in its degrees of clinical severity (laryngitis, laryngotracheitis, and laryngotracheopneumonitis) and the rhinopharyngeal flora of each group is separately tabulated (Table V) no one potential pathogen occurs in a sufficiently high incidence to justify its classification as an etiologic agent. This observation is likewise true when the 35 tracheotomized cases of so-called "virus"

TABLE V

SUMMARY OF RESULTS OF RHINOPHARYNGEAL CULTURES IN THE VARIOUS TYPES OF "VIRUS" CROUP

(Percent of Positive Cultures Obtained)

Organism	Laryngitis (161 Cases)	Laryngotracheitis (98 Cases)	Laryngotracheo-pneumonitis (38 Cases)
H. influenzae	40.4%*	42.8%†	47.3%*
H. str.	8.7%	9.2%	7.8%
Pneumococcus	44.2%	59.2%	68.4%

* One case had type B organisms. Clinical course and pathology indicated these bacteria were not responsible for the disease. The remaining organisms were either untyped, or not type B.

† Untyped or not type B.

TABLE VI

SUMMARY OF RESULTS OF RHINOPHARYNGEAL CULTURES IN TRACHEOTOMIZED AND FATAL CASES OF "VIRUS" CROUP

(Percent of Positive Cultures Obtained)

Organism	Tracheotomized (35 Cases)	Fatal (7 Cases)*
H. influenzae†	45.7%	57.2%
H. str.	22.8%	14.3%
Pneumococcus	68.6%	42.8%

* Cultures from one patient who died were not reported. Total fatal cases, eight.

† The cultures from one patient, tracheotomized and fatal, were positive for type B. Clinical course and living and morbid pathology indicated that this organism was not responsible for the disease.

croup are considered separately (Table VI). Although the incidence of hemolytic str. in tracheotomized cases of "virus" croup (23%) was higher than in any other category with this disease, the incidence was the same as that observed in cases with diphtheritic croup. None of the blood cultures of tracheotomized "virus" croup cases were positive for hemolytic str. It seems justifiable to state from these and previous observations that hemolytic str. have no etiologic significance in this infection.

The incidence of pneumococci in the tracheotomized cases of "virus" croup (69%) is again not sufficient to classify the organism as the etiologic agent in this disease. If

pneumococci were responsible for the pathology leading to tracheotomy one would expect a correlation between the occurrence of pneumococci in these cases and a high white blood cell count (Trask).[11] Such was not the case.

Ninety-seven percent of the tracheotomized cases represented more severe forms of croup (46% laryngotracheitis, 51% laryngotracheopneumonitis). Pneumococci occur in higher incidence in the more extensive forms of so-called "virus" croup (Table V) although the reason is not obvious. The importance of this occurrence, however, is minimized in view of the fact that only 43% of the fatal cases had pneumococci in the rhinopharynx (Table VI, column 2) an incidence which is not statistically different (Chi-square test) from that observed in normal patients (Table II). This comparatively low incidence of rhinopharyngeal pneumococci occurred in spite of the fact that 14% of the cultured fatal cases were classified as laryngotracheitis and 71%, laryngotracheopneumonitis.

The only case of bacteremia (due to pneumococcus type XIX) found among the so-called "virus" croup patients occurred in a tracheotomized case. The patient recovered and clinically the course was in no way different from tracheotomized cases in which this organism was absent from the rhinopharynx and blood. Thus, the role of the pneumococcus in so-called "virus" croup appears to be a minor one, although in some instances it accounts for a complication in the course of the infection.

The bacteriologic findings in the seven fatal cases of "virus" croup which were cultured,* emphasized the absence of any consistently appearing bacteria in this disease (Table V). Four of the fatal cases grew H. influenzae from the nasopharynx, and from three others pneumococci were recovered from the same location. One case had beta hemolytic str., Group B, in the rhinopharynx. (The appearance of this organism is not significant when one recalls the study by Boisvert[2] in which 262 pediatric patients affected with some form of obvious streptococcal disease yielded 509 strains of Group A hemolytic str., and no other group was obtained.) All of the seven patients had cultures of the blood. There were 12 antemortem cultures and five postmortem cultures. All were negative. It is, therefore, apparent that no correlation exists between mortality and the consistent appearance of any potential bacterial pathogen in this form of infectious croup.

The low incidence of positive blood cultures is strong evidence against the importance of bacteria in "virus" croup.† Of the 297 cases, 262 had admission blood cultures. Blood cultures were repeated as indicated, so that a total of 302 specimens of blood were cultured, including five postmortem cultures. Only one culture was considered to indicate a bacteremia. This was the case of pneumococcus type XIX bacteremia referred to previously. Nineteen of the blood cultures contained Staph. albus and diphtheroids. These are among the most commonly encountered contaminants, and there was nothing in the patients' course to indicate that their presence might possibly be of

---

* There were eight fatal cases. In one case death occurred shortly after admission and cultures of the rhinopharynx and blood were not reported.

† Review of cases from this clinic show the incidence of positive blood cultures in various diseases to be as follows: H. streptococcal pneumonia—21.7% (46 cases), pneumococcal pneumonia—14.7% (313 cases), H. influenzae type B croup—89.4% (28 cases), C. diphtheriae croup—18.2% (22 cases).

TABLE VII

RECOVERY OF BACTERIA FROM VARIOUS PARTS OF THE RESPIRATORY TRACT IN THE THREE ETIOLOGIC TYPES OF INFECTIOUS CROUP

Case No.	Organisms Recovered	Rhino-pharynx	Larynx	Trachea	Bronchi
			"VIRUS" CROUP		
1	No pathogens	+	+		
2	No pathogens	+	+		
3	No pathogens	+	+		
4	Pneumococcus XI	+	+		
5	H. str.	+	+		
	Pneumococcus XIX	+	+		
6	H. influenzae not typed	+	+		
7	Pneumococcus XXIII	+	+		
8	Pneumococcus XI	+	+		
	H. influenzae not typed	+	+		
9	Pneumococcus XV	+	+		
10	Pneumococcus V	+	+		
11	H. influenzae not typed	+		+	
12	Pneumococcus V	+		+	
13	H. str.	+		+	
14	Pneumococcus XIX	+		+	
	H. influenzae not typed	+		+	
15	Pneumococcus XVIII	+	+	+	+
	H. str.	+	*	+	
			H. INFLUENZAE TYPE B CROUP		
16	Pneumococcus XIX	+	+		
	H. influenzae type B	+	+		
17	Pneumococcus XXIII	+	+		
	H. influenzae type B	+	not typed		
18	H. influenzae not typed	+	+		
			DIPHTHERITIC CROUP		
19	C. diphtheriae	+	+		
20	C. diphtheriae	+	+	+	
21	C. diphtheriae	+		usual flora	
22	C. diphtheriae	+		+	
23	C. diphtheriae	+		+	
	H. str.	+		+	
24	C. diphtheriae	+		+	
	Pneumococcus V	+		+	

* H. str. not recovered.

Blank spaces indicate that no cultures were obtained from these sites.

significance. The incidence of bacteremia in so-called "virus" croup was, therefore, only 0.38%.

Finally, we must consider the relationship between rhinopharyngeal and laryngotracheal cultures in infectious croup. Table VII shows the correlation between the two sources of culture material. It is clear that the rhinopharyngeal cultures reflect accurately the flora of the larynx and trachea.

Leukocytes in "Virus" Croup: In Chart I the incidence of admission WBC in various numerical groups is shown. There was no correlation between these numerical groups and the various potential pathogens recovered by rhinopharyngeal culture. Eighty-seven percent of the counts were below 20 thousand, 27% were below 10 thousand, and 69% were between 5 and 15 thousand. In view of the relatively low counts in a disease often so fulminating, a virus etiology is intimated.

Discussion

It became apparent to us a few years ago that there was such great diversity among definitions of the entity infectious croup, on the one hand, and such unfounded specificity attached to the terms laryngitis, laryngotracheitis and laryngotracheobronchitis on the other hand, that the concept of infectious croup as a specific disease entity was almost meaningless. For this reason the endeavors which culminated in this and other reports[6, 7] were undertaken.

The definition of acute infectious croup used in this work was sufficiently specific to cause no difficulty in choosing cases, and yet was general enough to include numerous etiologic groups. One of the most enlightening results of definition and classification was to show that laryngitis, laryngotracheitis, and laryngotracheopneumonitis were merely clinical terms, and as such were useful prognostic guides. As terms indicating etiology they proved to be worthless.

The validity of the etiologic classification of infectious croup into three groups will be supported in future papers describing the pathology and clinical course of two of these groups.[6, 7] However, the bacteriologic findings alone in the two groups defined as diphtheritic croup and H. influenzae type B croup leave little room for doubt as to the propriety of such a classification. The etiologic agent responsible for the remaining 297 cases comprising this study was not so easily determined. These cases presented a symptom complex, course, and pathologic picture different from that of croup due to H. influenzae type B or C. diphtheriae. However, no conclusive correlation could be found between the results of bacterial cultures of the rhinopharynx and any of the following: extent of the disease, incidence of tracheotomy, mortality, or blood counts. Only one positive blood culture (pneumococcus XIX) was found in a disease in which the most severe form (so-called "virus" laryngotracheopneumonitis) exhibits a mortality of 16%. It was therefore inferred that the type of croup represented by these 297 cases is induced by a non-bacterial agent. It was furthermore evident that even the most extensive form of the disease is little influenced by the rhinopharyngeal flora but instead is dependent upon the primary etiologic agent plus constitutional factors such as age of the child, size of the larynx, duration of the disease, and development of immunity.

What is now most needed in the study of this disease is the application of technics designed to elucidate the non-bacterial agent or agents which appear to initiate so-called "virus" croup.

Conclusion

Acute infectious croup can be divided into three etiologic categories; namely, diphtheritic croup, H. influenzae type B croup, and so-called "virus" croup. The clinical divisions of this disease, i.e., laryngitis, laryngotracheitis, and laryngotracheopneumonitis, are of prognostic value, but have no etiologic significance.

ACKNOWLEDGEMENTS

The author wishes to acknowledge the valuable advice and criticism given him in the preparation of this paper by Dr. Grover F. Powers, Dr. Paul L. Boisvert, and Dr. Donal Dunphy.

REFERENCES

1. Poole, F. D., and Fousek, M. D., Etiologic diagnosis of pneumonia in children by rapid typing of nasal cultures, J.A.M.A. **113**:1854, 1939.
2. Boisvert, P. L., Human hemolytic streptococci from diseases of children, Am. J. Dis. Child. **59**:281, 1940.
3. MacNab, J. C. G., Acute streptococcal infection of trachea in an infant, aged 15 months, J. Laryngol., Rhinol., and Otol. **30**:336, 1915.
4. Neffson, A. H., Acute laryngotracheobronchitis, 25 year review, Am. J. M. Sc. **208**:524, 1944.
5. Williams, H., Melbourne, Australia, Personal communication.
6. Rabe, E. F., Infectious croup. II. "Virus" croup, Pediatrics, in press.
7. Rabe, E. F., Infectious croup. III. Hemophilus influenzae type B croup, Pediatrics, in press.
8. Sinclair, S. E., H. influenzae type B in acute laryngitis with bacteremia, J.A.M.A. **117**:170, 1941.
9. Yang, H. S., Nasal flora of children in day nursery, Am. J. Dis. Child. **61**:262, 1941.
10. Heffron, R., Pneumonia with Special References to Pneumococcus Lobar Pneumonia, The Commonwealth Fund, New York, 1939. p. 1.
11. Trask, J. D., Pneumonia and bronchitis, Brenneman's Practice of Pediatrics, Vol. 2, chapter 48, W. F. Prior Company, Inc., Hagerstown, Md., 1940, p. 22.

SPANISH ABSTRACT

Crup Infeccioso. I. Etiologia

Este trabajo esta basado en un estudio de 347 casos de crup infeccioso. El crup infeccioso se define como una enfermedad del tracto respiratorio alto, caracterisado por imflamación de la rinofarinx con deseminación descendente de la infección que conduce a variables grados de estenosis de las vias aereas laringea, laringotraqueal or laringotraquebronquial. Esta estenosis es debido a edema y es ocasionalmente agravada por formaciones membranosas.

Basandose en signos y sintomas reconocidos, el crup infeccioso fue dividido en tres grupos clinicos; a saber: laringitis, laringotraqueites, y laringotraqueopneumonitas. Tal clasificación demostró tener significación pronostica, pero no etiologica, para los casos individuales. Relacionando la bacteriologia, patologia y curso clinico de los casos, el crup infeccioso fue divido en tres distintos categorias etiologicas; a saber: crup difterico, crup H. influencia tipo B, y el llamado "virus," o crup no bacteriano.

789 Howard Ave.

TREATMENT OF AN INFANT WITH PAROXYSMAL AURICULAR TACHYCARDIA

By ROBERT L. MOORE, M.D.
Dallas, Texas

HUBBARD[1] has reviewed 19 cases of paroxysmal tachycardia in infants under one year of age which had been reported prior to 1941, and added nine additional cases. He thought that the condition was probably much more frequent than commonly realized. Substantiating this, is the fact that since then there have been at least 16 additional cases reported.[2–13] However, it is probably rare enough to cause the diagnosis to be overlooked in many instances, because it is not considered a possibility when one is confronted with abnormally rapid heart rates in infants, particularly during the newborn period. An additional case seems worth reporting because it illustrates this fault, and because it presents some interesting problems which have not been described in the previously reported cases.

L. F. R., Jr. was seen by us for the first time at the age of 18 days because of attacks of cyanosis. He was born at term. The pregnancy and delivery were normal. He cried spontaneously and his color was normal. He was examined on the first day of life and remained in the hospital one week during which time he had no difficulty. During the night after the baby arrived home, he became cyanotic, breathed rapidly and was very restless. The next day his color seemed normal, but he was restless all day. The second day after the cyanotic attack, he was taken to see his doctor because he was irritable and was vomiting some of his feedings. A chest film at this time showed an enlarged supracardiac shadow, and because this was interpreted as an enlarged thymus, he was given a therapeutic dose of X-ray over the mediastinum. Again, that night the baby became cyanotic with rapid and labored respirations. He was given O_2 by funnel, but the respiratory difficulty continued most of the night. A similar attack occurred the next day and on the following day he was given another X-ray treatment. That evening he had a fourth attack. A third X-ray treatment was given four days later and that evening a fifth attack of cyanosis occurred. A repeat film of the chest showed that the thymus shadow had decreased in size and no further X-ray treatments were deemed necessary. Two days later a sixth attack of cyanosis occurred with again the story of respiratory difficulty.

We were asked to see the baby on this day. He was a well developed, well nourished baby of 18 days. He was pale, and listless and irritable. There was no cyanosis. Respirations were not rapid or labored. The heart was rapid, but not unduly so. Heart sounds were normal. There were no murmurs. The abdomen was soft and the liver and spleen were not enlarged. The baby seemed hypotonic. Considered as diagnoses were intracranial damage at birth, congenital cerebral defect, atelectasis or congenital anomaly of the heart. Listlessness was due to phenobarbital which was given because of irritability and vomiting.

He was seen again that night during an attack. He was moderately cyanotic, respirations were rapid, irregular, and slightly labored. The heart was so rapid the rate could not be counted accurately. It was estimated to be 200 or above. The lungs were clear. The baby was given oxygen and before morning the attack ceased. The next day he had another attack, which did not stop. By the next afternoon when his color became much worse the baby was admitted to the hospital.

On admission the cyanosis was marked. The respirations were at times as high as 80/min. The temperature was 38.9° C. He was put in an oxygen tent and, because pneumonia seemed a possibility, was given penicillin, 5,000 units intramuscularly every three hours. His blood count on admission revealed WBC 19.6 thousand with 71% polynuclear neutrophiles. Hgb. was 18 gm./100 cc. blood. Urine was normal.

From the Department of Pediatrics, Southwestern Medical College and the Children's Medical Center.

(Received for publication May 22, 1948.)

The next day the baby improved somewhat. The temperature was normal and his color, while in the O_2 tent, was good. However, his respirations remained between 80 and 100/min. The heart rate continued to be over 200/min.

Two days later there were definite signs of heart failure, the heart increased in size, and the liver became progressively larger. His color was poor, but cyanosis was not so marked as on admission. By the sixth hospital day WBC was 9 thousand with only 38% polynuclears. Penicillin was discontinued. By this time edema had developed. Roentgenogram of the chest (Fig. 1) showed a large water bottle shaped heart which suggested the possibility of pericardial fluid. There was some atelectasis, particularly in the right lower lobe.

By the ninth hospital day and the eleventh day of the attack, there was generalized edema, the liver was down almost to the iliac crest and there were rales at the lung bases. The heart and respiratory rate were still tremendously rapid and the color was poor. Digitalization was begun by

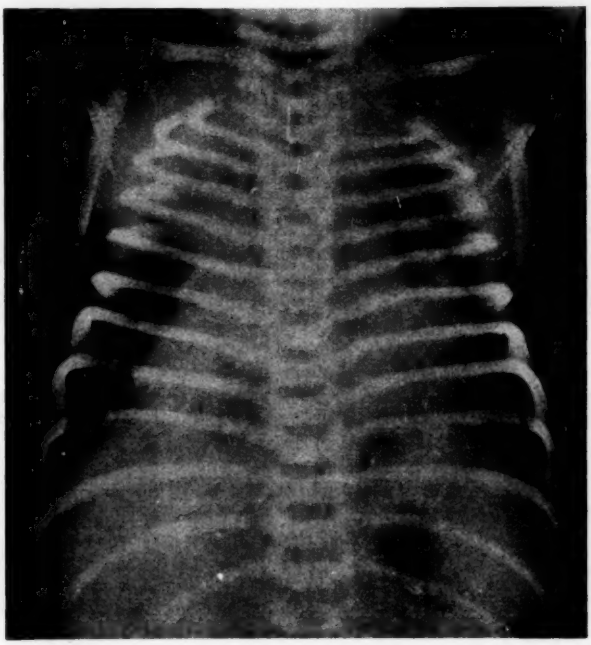
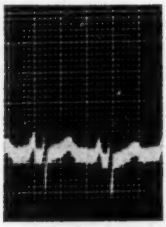


FIG. 1. Tremendous enlargement of heart which was due to prolonged paroxysm of tachycardia.

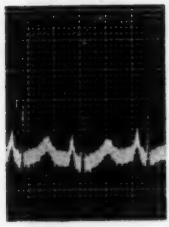
mouth. Estimating his weight without edema as 3.6 kg. and using 0.2 cc./kg. of the tincture, we gave 0.1 cc. by mouth for the first dose. A second similar dose was given two hours later and then 0.1 cc. every four hours thereafter. By the time he had had 0.6 cc. of the tincture he improved. His color was better by the end of 18 hours and the heart rate could be counted at 160 to 180/min. The respirations, which had been over 80, dropped to 40 to 50/min. This was 12 days after the onset of the attack. From that time on his improvement was steady. Diuresis began on the second day after beginning digitalis and the edema was gone completely seven days after treatment was started. On this day he was removed from the oxygen tent. Three days after digitalis was started an electrocardiogram (Fig. 2) showed a rate of 115/min. and right axis deviation. The liver and heart decreased in size progressively. A roentgenogram five days later showed a heart almost normal in size and contour and a disappearance of the atelectasis at the right base. After eight doses of digitalis every four hours, it was decreased to 0.1 cc. once daily. He remained on this dosage and was discharged home after 27 days in the hospital. On discharge his physical examination was

entirely normal. The respirations were slow and regular. The heart rate was 100 to 120/min. The heart was normal in size.

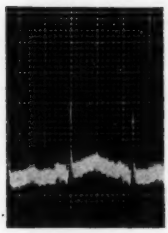
He continued well at home for nine days when he again became cyanotic, dyspneic and had marked tachycardia. Dr. Tinsley Harrison saw him and thought the diagnosis was paroxysmal tachy-



Lead 1

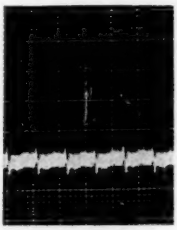


Lead 2

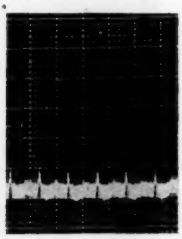


Lead 3

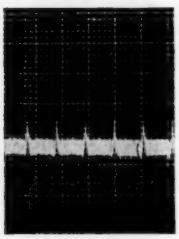
FIG. 2



Lead 1



Lead 2



Lead 3

FIG. 3

FIG. 2. Normal electrocardiogram showing rate of 115/min. and right axis deviation. Taken after first severe attack had terminated.

FIG. 3. Electrocardiographic tracing made during attack. Ventricular rate—274.

cardia, and an electrocardiogram (Fig. 3) was made and confirmed this impression. Carotid sinus pressure, pressure on the eyeballs, and gagging the baby failed to alter the rate, which was shown to be 274/min. The digitalis, which the baby had been taking continuously was increased to 0.2 cc. every four hours. He was also given phenobarbital and oxygen. After 24 hours the rate was still as rapid as before and the baby had begun to vomit. The dosage was cut to every 12 hours. Two days later signs of heart failure were beginning again and, since digitalis seemed not to be terminating the attack, it was decided at Dr. Harrison's suggestion to try the effect of acetyl-beta-methylcholine (mecholyl chloride). The baby was given 0.5 mg. intramuscularly. We were listening

to the heart at the time of the injection. Within 30 seconds after the drug was administered the baby became pale and cold as though in shock. He salivated profusely. The respirations became labored. The heart suddenly slowed from its previous rate of 270/min. to no more than 40 or 50 beats/min. These sounds were difficult to hear because there were asthmatic wheezes throughout the chest. Within two minutes the baby was flushed and gagging. The respirations were still labored and the heart rate slow. At this time he was given 0.065 mg. of atropine intramuscularly. Within a few minutes the baby appeared improved. The respirations became easier. The heart rate gradually rose to 140/min. and stayed there. The effects of the injection were not completely gone for 30 to 45 minutes. The baby was kept on 0.2 cc. of tincture of digitalis daily and was kept in the hospital for five days longer. His pulse rate remained 100 to 120/min., and he seemed perfectly normal. Electrocardiogram showed no abnormalities.

He went home on 0.2 cc. tincture of digitalis per day; and, except for occasional spells of vomiting, he did well. He gained weight rapidly and for four weeks had no known attacks.

When he was three months old, he started another typical paroxysm. Again, increasing the digitalis to the point of vomiting failed to stop the attack, and, on the third day, when cardiac failure seemed to be beginning again, he was given acetyl-beta-methylcholine 0.25 mg. with no results. Thirty minutes later 0.5 mg. were given, and after another 30 minute interval 1.5 mg. were given and except for slight increase in salivation there was no result. When 2.0 mg. were given, the reaction was exactly similar to the original response with only 0.5 mg. The baby seemed for a few minutes as though he might die, but improved rapidly when atropine was given, and the paroxysm was definitely stopped.

For about three weeks no attacks occurred. He continued on tincture of digitalis 0.2 cc. twice daily. Then he awakened in the morning with another attack. Because of the severity of the reaction to acetyl-beta-methylcholine, it was decided to try quinidine first. He was given quinidine 20 mg. orally without effect. Two hours later this was increased to 40 mg., then 60 mg., 80 mg., 100 mg., and finally 120 mg. before the attack subsided. He was kept on 20 mg. of quinidine every four hours, and there were no paroxysms until a month later when he had another attack. This was stopped with a dosage of 120 mg. The next day another attack occurred which needed 140 mg. to stop it. Three days later 180 mg. was needed to stop a paroxysm. His daily dosage was increased to 40 mg. every four hours.

A week later he began to have attacks frequently. Four paroxysms occurred the following week. Quinidine in a dose of 140 mg. stopped these rather promptly. Four days later he had two attacks. This was the first time he had had more than one paroxysm in 24 hours. He then had five more attacks in the next six days. Two days later he had another paroxysm, which was the thirty-first since the age of eight days. He was now five months and 19 days old. This took 200 mg. of quinidine to terminate it, but from that time until the present he has had no definite attacks. In December 1946 he may have had another short paroxysm but, if so, it lasted only a few minutes. He was kept on digitalis until the age of 11 months. His development has been normal. He has tended to be larger and heavier than the average. At one year of age he weighed 11.9 kg. and was 77.5 cm. tall. At two years he weighed 14 kg. and was 89 cm. tall. Except for his attacks of tachycardia, his only illnesses have been two mild respiratory infections. He is now 25 months old.

Discussion

Hubbard has pointed out the mistakes in diagnosis which he thinks are frequently made. He mentions particularly congenital idiopathic hypertrophy of the heart and pneumonia. We made both of these errors of diagnosis in this instance. In addition this baby had previously been said to have an enlarged thymus, which was treated. We have always tended to doubt this diagnosis and we wonder how many attacks of cyanosis in newborns, for which the thymus has been blamed, are actually episodes of paroxysmal tachycardia, which spontaneously subside.

In spite of the frequency with which the diagnosis is undoubtedly missed, it should be easy to make, provided one keeps the possibility in mind. Because infants' normal heart rates are rapid and variable, and because mild febrile illnesses or other disturbances

so easily cause a marked tachycardia, one is apt not to think of a rapid heart as being a primary disturbance.

A remarkably consistent clinical picture seems to occur in this condition and should lead one to consider paroxysmal tachycardia as a possibility. The baby at first becomes restless. His respirations are remarkably rapid, at times 100/min. or more. Cyanosis and pallor occur. The restlessness soon gives way to listlessness. Vomiting is frequently present. Sometimes there is some fever and leukocytosis. If spontaneous relief from the attacks does not occur, signs of congestive failure develop which may lead to death.

The etiology of this condition is not known. There is much discussion concerning the differentiation between auricular flutter and paroxysmal tachycardia, but for practical purposes this need not disturb us. In this baby we failed to find anything that seemed to precipitate the attacks. At one time the mother believed that the baby had them only when he was on his abdomen and raised his head and shoulders. But we soon discovered that he would have attacks while she kept him on his back. It is said that nervousness and excitement bring on the attacks. Most of the attacks this baby had started during the night while he was asleep and completely relaxed. There was no relationship to crying or intake of food.

The most troublesome aspect of this case was the problem of treatment. Hubbard and others have advocated digitalis as the best means of stopping the attacks. Certainly digitalis was a life saver in his first severe paroxysm. However, digitalis was disappointing after its first successful use. It failed to prevent attacks or to terminate later ones. The dosage of digitalis was not large but when vomiting occurred we did not feel justified in increasing the drug further. The baby was on digitalis almost constantly until 11 months of age, and it may have prevented him from having daily attacks.

The most dramatic means of stopping the paroxysms was by the use of acetyl-beta-methylcholine hypodermically. Morgan[15] in 1943 advocated its use in persistent paroxysms. On the two occasions in which it was used in this infant the reactions were exactly the same, but the dose necessary to secure results varied tremendously. The second administration of acetyl-beta-methylcholine, which took about four times as much to bring about the desired results, was given on the morning after quinidine had been used the day before. Quinidine is known to inhibit the action of the former drug, but, in the 24 hours which had elapsed since quinidine had been given, all quinidine effect should have been gone. If one bears in mind the violent reactions, and begins with small doses and increases these slowly until the desired effect is obtained; and, above all, if atropine is kept at hand to stop the action if necessary, this is a most valuable drug in treating paroxysmal tachycardia.

Oral administration of this drug has been found useless in both treatment and prevention. We used it orally for a few days without results.

Quinidine[16] has been used extensively both orally and intravenously in terminating prolonged paroxysms. Quinidine proved to be very useful in stopping attacks in this case, but less useful in prevention. The baby gave no evidence of toxic effects. It probably should only be given orally and, if parenteral medication is needed, acetyl-beta-methylcholine should be used.

Various other drugs have been used, including quinine, ipecac, apomorphine, prostigmine and pentamethylene tetrazol (metrazol). Since the paroxysms could be controlled by the other three, none of these was tried.

Summary

Paroxysmal tachycardia occurs more frequently in infants, than is generally recognized; and, undoubtedly, is frequently misdiagnosed.

A case is reported of an infant who had 31 attacks of paroxysmal tachycardia between the ages of eight days and five and a half months. Many of the paroxysms would not stop spontaneously and heart failure would occur.

Quinidine, acetyl-beta-methylcholine, and digitalis were all found to be effective in controlling the attacks. The first two seemed to be more effective than the last. Because of the violent reaction to acetyl-beta-methylcholine, it is thought best to use this method only if the other two fail to bring relief.

References

1. Hubbard, J. P., Paroxysmal tachycardia and its treatment in young infants, Am. J. Dis. Child. **61**:687, 1941.
2. Hobbs, L. F., Paroxysmal tachycardia in infancy, Am. Heart J. **21**:804, 1941.
3. Hubbard, J. P., and Starbuck, G. W., Paroxysmal tachycardia in two month old infant with ventricular rate of 350, Am. J. Dis. Child. **65**:582, 1943.
4. Tarnower, H., and Lathin, B., Tachycardia in newborn, New York State J. Med. **42**:805, 1942.
5. Blanchford, and Hoppe, Paroxysmal tachycardia in young infants, J.M.A. Georgia **32**:47, 1943. 47, 1943.
6. Keagy, A. M., and Magee, R. S., Supraventricular tachycardia in infancy, Penn. Med. J. **45**:44, 1941.
7. Young, J. H., Paroxysmal tachycardia in infant, Med. J. Australia **1**:538, 1944.
8. Howard, P. W., Paroxysmal tachycardia in infant fourth day of life—recovery with digitalis, J. Pediat. **26**:273, 1945.
9. Bloom, N., and Kendig, E. L., Jr., Extreme paroxysmal supraventricular tachycardia, J. Pediat. **28**:474, 1946.
10. Scott, E. P., and Lumper, Margaret A., Paroxysmal tachycardia, J. Pediat. **28**:96, 1946.
11. Vezina, N., Paroxysmal tachycardia with rate of 350 beats a minute in four months old infant, Union Med. du Canada **73**:648, 1944.
12. Newbauer, C., Paroxysmal tachycardia in infancy and childhood, Brit. Heart J. **7**:107, 1945.
13. Arana, M. R., and Kreutzer, R., Paroxysmal tachycardia in newborn successfully treated with intravenous neostigmine, Arch. Argent de Pediat. **19**:405, 1943.
14. Grollman, A., and Slaughter, D. H., Cushny's Pharmacology and Therapeutics, 13th Edition, Lea and Febiger, Philadelphia, 1947, p. 449.
15. Morgan, P. W., Management of paroxysmal tachycardia including use of mecholyl, Ann. Int. Med. **19**:780, 1943.
16. Sturnick, M. J., Riseman, J. E. F., and Segall, E. L., Studies on action of quinidine in man, J.A.M.A. **121**:917, 1943.

Spanish Abstract

Tratamiento de la Taquicardia Paroxistica en un Niño

La taquicardia paroxistica en el niño es mas frecuente de lo que generalmente se cree; y es sin duda frecuentemente diagnosticada erroneamente.

Se describe el caso de un niño que tuvo 31 ataques de taquicardia paroxistica entre las edades de ocho dias y cinco meses y medio. La mayoría de los paroxismos no cesan espontaneamente, sobreviniendo fallo cardíaco.

La quinidina, acetil-beta-metilcolina y digital fueron efectivas para controlar los ataques. Las dos primeras parecieron actuar mas efectivamente que la última. Debido a las violentas reacciones de la acetil-beta-metilcolina, se cree mejor usar este metodo solamente en los casos en que aquellas no proporcionaron mejoria.

3403 Hall Street at Turtle Creek Blvd.

OLIGODYNAMIC ACTION OF METALLIC ELEMENTS AND OF METAL ALLOYS ON CERTAIN BACTERIA AND VIRUSES

I. In Vitro Observations

By CHARLES F. McKHANN, M.D., HARVE J. CARLSON, D.P.H., AND HARRIET DOUGLAS, B.S.
Cleveland, Ohio

THE OLIGODYNAMIC action of metals and metal compounds was noted in 1893 by von Naegeli[1] who pointed out that "definite metals and metal compounds confer in minute quanity of water solutions the ability to change and finally kill cells in a characteristic way." Many metallic elements have been observed to inhibit the growth of bacteria[2-10] and to inactivate enzymes.[11-13, 16, 8] Practical application of such activity of metals has been made in the purification of water[14, 15] and in the preservation of tomato juice,[16] of cider,[17] and of hides.[18]

Metallic lead, cadmium, and mercury have been noted to exert an oligodynamic action[19-23] at varying distances from micro-organisms, apparently the result of solution of small amounts of individual ions in the medium. Minute amounts of certain metals have been found to stimulate the growth of tumors in rabbits.[24]

Although the virus of poliomyelitis[25-31] and that of influenza[32-34] have been shown to be inactivated *in vitro* by salts of heavy metals, studies with viruses similar to those made on the oligodynamic action of metallic elements on bacteria are not available. Furthermore several metals are now obtainable which were not included in earlier studies.

The purpose of this report is to present the results of investigations of the possible oligodynamic action of metallic elements and metal alloys on various species of bacteria and fungi, and on the viruses of poliomyelitis (Lansing strain) and on influenza A (PR8) by *in vitro* methods. Table I depicts the periodic arrangement of the elements and a list of the metals employed.

MATERIALS AND METHODS

Metallic elements and alloys: The metallic elements were obtained in so far as possible as pure substances, but manufacturers' analyses were accepted and no attempts were made to ascertain if there might be traces of impurities present. The manufacturers' analyses of the composition of some of the metal alloys are listed in Table II with amounts of each ingredient stated on a percentage basis.

Solid pieces of pure metal or alloy were thoroughly cleansed with detergent, weak acid or alkali solutions, and with other agents that would not be likely to cause chemical change on the surface of the metal, to remove grease film or other protective surface covering. The metals were removed from the cleansing solutions with forceps and were

From the Department of Pediatrics, Western Reserve University School of Medicine and the Babies and Childrens Hospital of Cleveland, Ohio.

Supported in part by a grant from Lederle Laboratories, Pearl River, N.Y.
(Submitted for publication May 25, 1948.)

TABLE I

PERIODIC ARRANGEMENT OF ELEMENTS TESTED FOR OLIGODYNAMIC ACTIVITY

Series	Period	Zero Group	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII	Group VIII
0										
1										
2	1			Beryllium						
3	2			Magnesium	Aluminum	Silicon				
4						Titanium	Vanadium	Chromium	Manganese	Iron, Cobalt, Nickel
5	3			Zinc	Gallium			Selenium		
6			Copper		Yttrium	Zirconium	Columbium	Molybdenum		Ruthenium, Palladium
7	4									
8			Silver	Cadmium	Indium	Tin	Antimony	Tellurium		
9	5					Cerium				
10							Tantalum	Tungsten	Rhenium	Osmium, Indium
11	6									
12	7		Gold	Mercury	Thallium	Lead	Bismuth			

rinsed in tap and distilled water. Powders or filings were treated with a similar cleansing process. Metals that were subject to rapid oxidation were polished to smooth bright surfaces on a high speed abrasive wheel. The clean metals were placed in dry glass receptacles and were sterilized by dry heat or in the autoclave for 20 min. at 15 lb. pressure. Alloys or elements that were pyrrophoric were sterilized by intermittent flowing steam on three successive days. Samples of the alloys and metallic elments were placed

TABLE II

ANALYSIS OF METAL ALLOYS

(1) Steel #4615 SAE—Approximate composition—
C. 0.10–.20, Mn. .4–.7, Ni. 1.65–2.0, Mo. 0.2–.3, P. .040 (max), S. .05 (max). Fe remainder.
(2) Aluminum alloy 24ST
Cu. 4.5, Mn. 0.6, Mg. 1.5, Al. remainder.
(3) Brass 85/15
Cu. 85, Zn. 15.
(4) Brass 70/30
Cu. 70, Zn. 30.
(5) Steel—4140 SAE.
C. .35–.45, Mn. .6–.9, Cu. .8–1.1, Mo. .15–.25, P. .040 (max), S. .050 (max). Fe. remainder.
(6) Steel—1.30C
C. 1.3, Mn. .25–.50, P. .040 (max), S. .050 (max), Fe. remainder.
(7) Steel—.50C
C. .50, Mn. .6–.9, P. .045 (max), S. .055 (max), Fe. remainder.
(8) Steel—Stainless
Cu. 18.0, Ni. 8.0, Fe remainder.
(9) Almel
Ni. 95, Remainder Si., Mn., Al.
(10) Nichrome
Ni. 65, Cr. 10, Fe. 15, Remainder Mn. Si.
(11) Chromel
Ni. 80, Cr. 20.
(12) Constantan
Cu. 44, Ni. 35, Remainder Mn., C., Fe.
(13) Monel
Ni. 67.0, Cu. 30, Fe. 1.4, Remainder Si., Mn., C.

in distilled water, buffered and non-buffered saline solutions, lung and brain tissue suspensions (1-200) for one and three hour periods to determine effects of the metals on various solutions, since any subsequent effect on bacteria or viruses might be in part traceable to a change in the medium, especially to partial coagulation or precipitation of the medium with changes in chemical reaction. Changes in pH of the various media on contact with different metals and alloys are shown in Table III.

It is to be noted that several metals induced changes in pH of the media which might well be factors in any observed effect of such metals on bacteria or viruses.

Bacteria and fungi subjected to exposure to metals were from 18 to 24 hour cultures which had been subcultured in liquid media several times before experimental use. One Ml. of liquid culture was inoculated into 250 Ml. of sterile nutrient or enriched agar, depending upon the growth requirement of the micro-organisms under test. The inoculum was thoroughly mixed into the agar and 15 to 20 Ml. amounts were poured into sterile

petri dishes. The tops of the petri dishes were left ajar for 30 to 45 min. to allow drying of the agar surface.

Preparation of viruses: The PR8 strain of influenza A virus, mouse and egg-adapted, and the mouse-adapted Lansing strain of poliomyelitis virus were used. The strains of each virus had been passed numerous times in mice and the PR8 egg-adapted strain of influenza virus had been through many passages in the chick embryo.

Allantoic fluid from infected chick embryos served as the source of influenza virus in the metal-neutralization experiments in chick embryos. Lungs showing 50% or more consolidation following inoculation of mice with PR8 strain were used as the source of the influenza virus for metal-neutralization experiments in mice. Brains and cords of mice which had become paralyzed two to eight days after inoculation were used as the source of poliomyelitis virus. Chick embryo allantoic fluid and mouse lungs infected with influenza virus and mouse brains and cords infected with poliomyelitis virus were stored in a dry-ice cabinet at a temperature approximating −72°C.

Methods of testing effect of metals on bacteria and fungi: Larger pieces or powders of metals and alloys were placed directly on the surface of seeded agar plates. Solid large pieces of metal were placed in the petri dishes containing liquid or semi-solid media. After incubation at 20 to 24°C. and 37°C. for 24 to 72 hours, zones of stimulation or inhibition were noted.

Methods of testing activity of metals on viruses: Influenza A egg-adapted: A 5×10^{-3} dilution of clear allantoic fluid containing the virus in buffered saline was added to sterile pieces of metals or powders in test tubes. The amount added depended upon the amount of metal present; sufficient virus suspension was added to cover completely solids and in the case of powders, sufficient solution was layered over to approximate an equal depth. Metal-virus suspensions were incubated at room temperature with frequent mixing for ½ to three hours. Four or more ten-day-old embryos were injected with 0.3 Ml. of the virus-metal suspension into the allantoic space through a small hole above the air sac. The injection site was sealed with paraffin-wax solution and the eggs were incubated at 37°C. for 48 hours. Observations were made at 48 hours and every 24 hours thereafter by candling to ascertain death of the embryo which was used as the end-point in these experiments. To verify the candling technic all eggs were opened.

Influenza A (mouse-adapted) virus suspension was diluted 2×10^{-2} in saline or buffered saline. The metal-virus suspension in amounts of 0.05 to 0.1 Ml. was inoculated into mice intranasally under light ether anesthesia. Mice succumbing to the infection were examined for pulmonary involvement; the animals surviving on the tenth day were sacrificed and autopsied. Those that died are listed in Table V as D with a subscript denoting the day of death. The degree of pulmonary involvement in the animals sacrificed on the tenth day is by numerals, with four plus indicating lungs completely consolidated, three plus denoting ¾ consolidation, and so on.

Poliomyelitis: Mouse brain-cord suspensions were diluted 1:100 in saline, distilled water, or buffered saline and subjected to action of the metals as described. Tests for viability of the virus were made by intracerebral inoculation of mice under ether anesthesia with 0.03 Ml. of virus suspension. Mice were examined twice daily for evidence of paralysis. Those with demonstrable paralysis are listed in Table VII as P while those that died of respiratory distress without paralysis of extremities are listed as D.

TABLE III

HYDROGEN ION CONCENTRATIONS OF MEDIA IN CONTACT WITH METALLIC ELEMENTS AND METAL ALLOYS

Metal or Element	Water		Saline			Suspensions		Form of Metal Used
			Non-buffered		Buffered	Brain	Lung	
	1*	3*	1*	3*	1*	1*	1*	
Copper	7.0	7.25	8.35	8.70	7.15	7.70	7.30	Powder
Copper			7.0		7.00	8.40	8.00	Solid
Silver			7.3					Solid
Gold			7.6					Solid
Beryllium			8.4					Solid
Beryllium	9.12	8.65	9.65	9.10				Powder
Magnesium	10.00	10.20	10.40	9.80	12.50	10.10	10.10	Powder
Magnesium			9.5					Ribbon
Zinc	7.00	7.10	9.45	10.40	7.80	9.50	9.55	Powder
Zinc			9.60		7.50	9.50	8.50	Solid
Cadmium			8.5		7.00	8.50	8.10	Solid
Mercury	7.00	7.00	8.20	8.10	7.00	7.25	7.25	
Aluminum			7.75					Solid
Gallium	7.35		6.9					
Yttrium	10.25	10.40	10.20	9.75	7.50			Oxide
Indium	6.15	6.00	7.40	7.90	7.25	7.70	7.50	Powdered
Indium			7.95		7.00	8.30	7.90	Solid
Thallium			11.30					Solid
Silicon			7.90		7.00	7.80	7.70	Solid
Titanium	12.35	12.35	11.90	11.70	12.50	8.90	9.00	Powder
Zirconium	6.00	6.10	6.85	7.65				Powder
Tin			7.05					Solid
Cerium	6.83	10.1						Solid
Lead			7.85					Solid
Vanadium			7.90					Solid
Columbium			8.20		7.49	9.10	8.90	Solid
Columbium	5.50	5.95	7.50	8.00	7.0	7.60	7.20	Powdered
Antimony			6.98		6.0	7.20	7.80	Solid
Tantalum	10.00	10.00	9.30	9.15				Powdered
Bismuth			6.90					Solid
Bismuth	6.40	6.00	7.30	7.80				Powdered
Chromium	8.15	8.50	7.70	8.80				Powdered
Chromium	8.55	8.15	8.90	8.95				Powdered
Selenium	8.35	9.50	10.95	10.30	7.00	8.60	8.50	Powdered
Molybdenum			4.80					Solid
Tellurium	4.60	4.90	6.50	7.60				Powdered
Tungsten			6.30					Solid
Tungsten	5.40	5.80	6.50	5.90	7.00	8.20	7.02	Powdered
Manganese			8.00					Solid
Manganese	8.90	8.70	10.20	10.10				Powdered
Rhenium	6.60	6.68	7.85	7.60	7.00	7.10	7.30	Powdered
Iron	7.50	8.00	7.65	7.10				Powdered
Cobalt			8.20		7.15	9.05	9.00	Solid
Nickel			7.90		7.00	8.10	7.70	Solid
Ruthenium	9.0		7.5					

TABLE III—(*continued*)

Metal or Element	Water		Saline			Suspensions		Form of Metal Used
			Non-buffered		Buffered	Brain	Lung	
	1*	3*	1*	3*	1*	1*	1*	
Palladium	7.50	7.50	8.90	8.30				Powdered
Osmium	6.85	6.85	7.90	7.80	7.00	7.00	7.35	Powdered
Iridium	8.70	9.20	8.50	8.00				Powdered
Platinum	6.4		8.4					Solid
Steel			6.60					11 Solid
Brass (Lo Cu) 70/30	6.90	7.00	8.50	8.10	7.15	7.60	7.00	Powdered
Brass (Lo Cu) 70/30			7.20		7.00	7.90	8.10	Solid
Stainless Steel			7.80					19 Solid
Almel			7.00					26 Solid
Nichrome			6.90					27 Solid
Chromel			6.90					28 Solid
Constantan			6.60					29 Solid
Monel			8.50		7.00	8.10	7.90	30 Solid
Hg-Ag Amalgom			8.30					32 Solid
Dental Amalgom	7.00	7.00	8.00	8.00	7.00	7.00	7.20	60 Powdered
Stainless Steel	5.8	6.45	7.30	7.30	7.00	7.20	7.50	65 Powdered
Iron	8.10	9.10	10.20	9.80				66 Powdered
Iron	7.50	9.30	7.60	6.90				68 Powdered
Mischmetal	7.00		10.98					
Brass			8.40					Solid 85/15

Control Measurements
pH of distilled H_2O—7.0
pH of Normal Saline—7.0
pH of KH_2PO_4NaOH in 0.9% NaCl—7.0
pH of Brain suspension in Saline—7.02
pH of Lung suspension in Saline—6.9

* Time of exposure in hours.

At intervals suspensions of brains and cords of mice that died without developing paralysis of the extremities were inoculated into other mice to ascertain presence or absence of virus.

Results

The effects of 39 metallic elements and 20 metal alloys on the growth of eight species of bacteria, including Staphlyococcus aureus, Streptococcus pyogenes, Bacillus subtilis, Diplococcus pneumoniae type 18, Escherichia coli, Eberthella typhosa, Pseudomonas aeruginosa, and "Zoogleal" sp. and six species of fungi, Penicillium (Waksman), Aspergillus niger, Streptomyces griseus, Streptomyces sp., Aspergillus terreus and Trychophyton sp. were studied. The effect was demonstrated by placing the metals in solid or powder form on the surfaces of seeded agar. In order to facilitate comparisons an effort has been made to tabulate the results. In the left hand column (Table IV) are listed the

TABLE IV

THE EFFECTS OF VARIOUS METALLIC ELEMENTS AND ALLOYS ON SEVERAL BACTERIA AND FUNGI

Group	Metal or Alloy	*Staph. aureus*	*Str. pyogenes*	*B. subtilis*	*Dip. pneumoniae*	*Esch. coli*	*E. typhosa*	*Ps. aeruginosa*	"*Zoogleal*" sp.	*Penicillium* (*Waksman*)	*Asp. terreus*	*Asp. niger*	*Str. griseus*	*Streptomycetes* sp.	*Trychophyton* sp.
I	Copper	PD_3	CD_1	GD_3			S	PD_1	CPD_4				PD_2	CPD_3	
	Silver		CD_2	CPD_4	CD_3			PD_1							
	Gold														
II	Beryllium		CD_0	S	CD_1			CD_1							
	Magnesium				CD_1			PD_0		PD_2	S		S	S	
	Zinc		CD_0	CD_3				PD_1	CD_2	CD_3	CD_1	PD_1	CPD_3	CD_3	CPD_3
	Cadmium	PD_2	CD_3				PD_1	CD_1			CPD_1	CPD_4	CD_3	CPD_3	PD_2
	Mercury		CD_2	ACD_0	CD_3			CD_1		CPD_3					
III	Aluminum						S	CD_0S							
	Gallium														
	Yttrium (Oxide)		CD_2S		CD_4				CD_1	PD_1	CD_1	CD_3	PD_1	CD_1S	
	Indium		PD_2S		CD_3										
	Thallium	CD_3			SCD_1S			CPD_4	CD_4		CPD_4				
IV	Silicon														
	Titanium		CD_2						CD_0						
	Zirconium			S				S							
	Tin														
	Cerium												PD_1		
	Lead							CD_1	PD_0						
V	Vanadium		CD_2		CPD_3					PD_2			S		
	Columbium			S				PD_2							
	Antimony	PD_2	CD_3	CD_3		PD_1	CD_3	CPD_3					CD_4	CD_4	
	Tantalum	S						CD_0	S						
	Bismuth				CD_3				PD_2				PD_2	CPD_3	

VI	Chromium													
	Selenium					PD_1	PD_2		PD_2					
	Molybdenum			PD_0	S	CD_4S			PD_1				S	
	Tellurium	PD_2	CD_2	PD_1S		PD_2	S	CD_3	CD_4				CD_4	PD_4
	Tungsten	CD_2S			PD_2			IT-	CPD_4S					
VII	Manganese			PD_1S			S	S	PD_0S	CD_0		PD_1S	S-	S-
	Rhenium	CD_2		CD_1S		CD_1	PD_2	ITPP	CD_2S	PD_2		PD_0	CD_2	CD_2
VIII	Iron						PD_1							
	Cobalt	MC	PD_1S		CD_3	PD_3	CPD_3	CD_4	PD_2	CPD_1	PD_2	CD_4S	CD_4	CPD_3
	Nickel		CD_2											
	Ruthenium													
	Palladium			S										
	Osmium			S			S	CD_2						
	Iridium	S					CD_0	S						
	Platinum													
	Steel		PD_0						PD_2	CD_0	PD_2	CD_4S	CD_4	CPD_4
	Steel						IT	PD_1		CD_1	PD_1	CD_1	S	S
	Steel				CD_4									
	Steel													
	Steel													
	Steel			S								S		
	Aluminum Alloy													
	Brass		CD_1	CD_3	CD_4		PD_1		CPD_2		PD_1		PD_3S	CPD_3
	Cast Iron													
	Steel			S				SD_0				S	SD_0	S
	Almel						CD_2		S	CD_2			S	
	Nichrome				CD_3						PD_1			
	Chrome													
	Constantan	PD_1		PD_3S			PS				PD_1			
	Monel		CD_3		CD_4			CD_3	CPD_4			PD_1	S	CD_3
	Hg-Ag Amalgom													
	Mischmetal							IT						
	Iron													
	Dental Amalgom		CD_0	PD_2			CD_1		CD_3				CD_2	CD_1
	Iron							IT						PD_2

TABLE IV

THE EFFECTS OF VARIOUS METALLIC ELEMENTS AND ALLOYS ON SEVERAL BACTERIA AND FUNGI

Group	Metal or Alloy	*Staph. aureus*	*Str. pyogenes*	*B. subtilis*	*Dip. pneumoniae*	*Esch. coli*	*E. typhosa*	*Ps. aeruginosa*	"*Zoogleal*" sp.	*Penicillium* (*Waksman*)	*Asp. terreus*	*Asp. niger*	*Str. griseus*	*Streptomycetes* sp.	*Trychophyton* sp.
I	Copper	PD_3	CD_1	GD_2			S	PD_1	CPD_4				PD_2	CPD_3	
	Silver		CD_2	CPD_4	CD_3			PD_1							
	Gold														
II	Beryllium		CD_0	S	CD_1			CD_1							
	Magnesium				CD_1			PD_0		PD_2	S		S	S	
	Zinc		CD_0	CD_3				PD_1	CD_2	CD_3	CD_1	PD_1	CPD_3	CD_3	CPD_3
	Cadmium	PD_2	CD_3				PD_1	CD_1			CPD_1	CPD_4	CD_3	CPD_3	PD_2
	Mercury		CD_2	ACD_0	CD_3			CD_1		CPD_3					
III	Aluminum						S	CD_0S							
	Gallium														
	Yttrium (Oxide)		CD_2S		CD_4				CD_1	PD_1	CD_1	CD_3	PD_1	CD_1S	
	Indium		PD_2S		CD_3										
	Thallium	CD_3			SCD_1S			CPD_4	CD_4		CPD_4				
IV	Silicon														
	Titanium		CD_2						CD_0						
	Zirconium			S				S							
	Tin														
	Cerium												PD_1		
	Lead							CD_1	PD_0						
V	Vanadium		CD_2		CPD_3					PD_2			S		
	Columbium			S				PD_2							
	Antimony	PD_2	CD_3	CD_3		PD_1	CD_3	CPD_3					CD_4	CD_4	
	Tantalum	S						CD_0	S						
	Bismuth				CD_3				PD_2				PD_2	CPD_3	

VI	Chromium													
	Selenium					PD_1	PD_2		PD_2					
	Molybdenum			PD_0	S	CD_4S			PD_1				S	
	Tellurium	PD_2	CD_2	PD_1S		PD_2	S	CD_3	CD_4				CD_4	PD_4
	Tungsten	CD_2S			PD_2			IT-	CPD_4S					
VII	Manganese			PD_1S			S	S	PD_0S	CD_0		PD_1S	S-	S-
	Rhenium	CD_2		CD_1S		CD_1	PD_2	ITPP	CD_2S	PD_2		PD_0	CD_2	CD_2
VIII	Iron						PD_1							
	Cobalt	MC	PD_1S		CD_3	PD_3	CPD_3	CD_4	PD_2	CPD_1	PD_2	CD_4S	CD_4	CPD_3
	Nickel		CD_2											
	Ruthenium													
	Palladium			S										
	Osmium			S			S	CD_2						
	Iridium	S					CD_0	S						
	Platinum													
	Steel		PD_0						PD_2	CD_0	PD_2	CD_4S	CD_4	CPD_4
	Steel						IT	PD_1		CD_1	PD_1	CD_1	S	S
	Steel				CD_4									
	Steel													
	Steel													
	Steel			S								S		
	Aluminum Alloy													
	Brass		CD_1	CD_3	CD_4		PD_1		CPD_2		PD_1		PD_3S	CPD_3
	Cast Iron													
	Steel			S				SD_0				S	SD_0	S
	Almel						CD_2		S	CD_2			S	
	Nichrome				CD_3						PD_1			
	Chrome													
	Constantan	PD_1		PD_3S			PS				PD_1			
	Monel		CD_3		CD_4			CD_3	CPD_4			PD_1	S	CD_3
	Hg-Ag Amalgom													
	Mischmetal													
	Iron							IT						
	Dental Amalgom		CD_0	PD_2			CD_1		CD_3				CD_2	CD_1
	Iron							IT						PD_2

TABLE V

The *In Vitro* Effects of Metallic Elements and Alloys on the PR8 Strain of Influenza A Virus

Periodic Group	Metal or Alloy	pH of Metal Virus Suspension	Mice Employed to Detect Virus Exposed to Metal	Mice Inoculated with Virus Not Exposed to Metal	Remarks
I	Copper	7.0[1] 8.35[2]	D_5, D_5, D_5, D_6, D_4, 0	D_4, D_5, D_6, D_5, D_6, D_7	Solid—30 min. exposure
			2, 1, 1, 0, 0, 0	D_5, D_5, D_6, D_6, D_5, 4	Filings—1 hr. exposure
			D_4, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_5, 1, 1, 2, 0	D_3, D_4, D_4, D_4, D_4, D_4, D_5, 4, 4	Filings—35 min. exposure
II	Beryllium	9.1[1,2]	D_0, D_3, 3, 3, 2, 1	D_4, D_4, D_4, D_5, D_6, D_7	1 death treated not flu
	Magnesium	10.0[1,2]	D_3, 3, 3, 2, 2, 0	D_5, D_6, D_7, D_7, D_7, D_8	
	Zinc	7.0[1] 9.45[2]	0, 0, 0, 0, 0, 0	D_4, D_4, D_4, D_4, D_4, 4	
			D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_8, D_8, 3, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_3, D_4, D_4, D_4, D_4, D_5, D_5, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_8, D_8, 4, 4, 0, 0	Adult mice
	Cadmium	8.5[2]	D_5, D_6, D_6, D_8, 3, 3	D_5, D_6, D_7, D_7, D_7, D_8	Solid
	Mercury	7.0[1] 8.1[2]	D_4, D_4, D_5, D_6, 2, 2	D_4, D_4, D_4, D_5, D_5, D_5	
III	Yttrium		D_6, D_8, 2, 0, 0	D_4, D_4, D_4, D_4, D_4, 4	Oxide
	Indium	6.15[1] 7.5[2]	D_6, 3, 3, 3, 2, 2, 0, 0, 0, 0, 0, 0, L, L	D_4, D_4, D_4, D_4, D_4, 4	L = Lost
			D_4, D_5, D_5, D_6, D_5, D_5, D_5, 4, 4, 3, 3, 2, 2, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_3, D_4, D_4, D_4, D_5, D_5, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_7, D_8, D_8, 4, 4, 0, 0	Adult Mice
IV	Silicon	7.9[2]	D_5, D_5, D_5, D_5, D_7, +	D_4, D_4, D_4, D_5, D_5, D_7	
	Titanium	12.0[1,2]	0, 0, 0, 0, 0, 0	D_4, D_4, D_4, D_5, D_5, 4	
	Zirconium	6.0[1] 7.5[2]	D_5, D_5, D_5, D_7, 4, 2	D_5, D_5, D_5, D_5, D_5, 4	
			D_{11}, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0		Deaths not flu
			D_6, D_6, D_7, D_7, D_8, D_8, 4, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_2, D_4, D_4, D_4, D_4, D_5, D_5, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_8, D_8, 4, 4, 0, 0	Adult Mice
V	Vanadium	7.9[2]	D_3, D_3, D_4, D_4, D_4, D_5	D_4, D_4, D_4, D_5, D_5, D_7	
	Columbium	5.7[1] 7.5[2]	D_7, D_7, D_8, D_8, 2, 1	D_4, D_4, D_4, D_4, D_4, 4	
	Tantalum	10.0[1] 9.2[2]	D_8, 4, 2, 0, 0, 0, 0, 0	D_4, D_4, D_5, D_6, D_7, D_7, D_8, D_8	
	Bismuth	6.2[1]	D_6, D_6, D_7, 3, 2, 2	D_5, D_5, D_5, D_5, D_5, 4	
VI	Chromium	8.3[1] 8.2[2]	D_5, D_5, D_5, D_7, D_5, D_5	D_5, D_5, D_5, D_5, D_5, 4	
	Selenium	8.7[1] 10.5[2]	0, 0, 0, 0, 0, 0	D_4, D_4, D_4, D_4, D_4, 4	
			D_6, D_8, D_8, D_{10}, 4, 3, 2, 2, 2, 2, 2, 1, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0		

TABLE V—(*continued*)

Periodic Group	Metal or Alloy	pH of Metal Virus Suspension	Mice Employed to Detect Virus Exposed to Metal	Mice Inoculated with Virus Not Exposed to Metal	Remarks
			D_3, D_4, D_5, D_7, D_7, D_7, D_8, 4, 2, 2, 2, 2, 2, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_8, D_9, 4, 4, 0, 0	Adult Mice
	Tellurium	4.8[1] 7.0[2]	D_7, D_7, D_8, 4, 4, 4	D_4, D_4, D_4, D_4, D_4, 4	
			D_8, 4, 3, 3, 2, 2, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0		
			D_4, D_5, D_6, D_6, D_6, D_6, D_6, D_6, D_7, D_8, 4, 4, 3, 2, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_2, D_4, D_4, D_4, D_4, D_5, D_5, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_8, D_8, 4, 4, 0, 0	Adult Mice
	Tungsten	5.6[1] 6.3[2]	2, 0, 0, 0, 0, 0	D_5, D_5, D_6, D_6, D_8, 4	
			D_6, D_6, D_6, D_7, D_7, D_7, D_7, D_8, 4, 2, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_2, D_4, D_4, D_4, D_4, D_5, D_5, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_8, D_8, 4, 4, 0, 0	Adult Mice
VII	Manganese	8.7[1] 10.0[2]	3, 2, 2, 1, 0, 0	D_4, D_4, D_4, D_5, D_5, D_7	
	Rhenium	6.4[1]	0, 0, 0, 0, 0, 0	D_6, D_6, D_7, D_7, D_8, 4	3 hours
			0, 0, 0, 0, 0, 0	D_6, D_6, D_7, D_7, D_8, 4	1 hour
	Rhenium	7.7[2]	D_4, D_7, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1	D_4, D_5, D_5, D_5, D_5, D_5, D_{10}, 1, 1, 0	Death and Sacrificed Mice —Not flu
			D_5, D_6, D_6, D_6, D_6, D_{10}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_2, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_8, D_8, D_8, D_{10}, D_{10}, 0, 4, 4	Adult Mice
VIII	Iron	7.5[1]	D_4, D_7, D_8, D_8, 1, 2	D_4, D_4, D_7, D_7, D_8, 4	
		7.7[2]	D_6, D_{10}, 0, 0, 0, 0	D_3, D_5, D_6, D_6, D_7, D_7	
			D_4, D_5, D_6, 1, 3, 4	D_5, D_5, D_5, D_6, D_6, D_8	
	Ruthenium		D_4, D_5, D_6, D_6, 3, 1	D_5, D_5, D_5, D_6, D_6, D_8	
	Palladium	7.51	D_5, D_6, D_6, 2, 4, 3	D_5, D_5, D_6, D_6, D_6, D_8	
	Osmium	6.85[1] 7.8	0, 0, 0, 0, 0, 0	D_6, D_6, D_7, D_7, D_8, 4	
			0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_4, D_5, D_5, D_5, D_5, D_5, D_{10}, 1, 1, 0	
			D_5, D_5, D_7, D_7, D_7, D_7, D_8, D_8, 3	D_6, D_6, D_7, D_7, D_7, D_7, D_8, D_8, D_8, D_{10}, D_{10}, 0, 4, 4	Adult Mice
	Iridium	9.0[1] 8.2[2]	D_6, D_6, D_6, D_7, D_8, D_8, 4, 3	D_3, D_5, D_5, D_5, D_5, D_6, D_6, D_6	
	Brass	7.0[1]	0, 0, 0, 0, 0, 0	D_5, D_6, D_5, D_5, D_5, 4	Lump 70/30
		8.3[2]	D_6, D_6, D_6, D_8, 4, 1, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	D_2, D_4, D_4, D_4, D_4, D_5, D_5, D_5, D_5, D_5, D_5, D_6, D_6, D_6, D_6, D_6, D_6, D_7, D_7, D_7, D_8, D_8, 4, 4, 0, 0	Adult Mice
Steel		6.1[1]	D_6, D_6, D_6, D_6, D_6, 1	D_5, D_6, D_6, D_6, D_6, D_6	Stainless 18–8 100 Mesh

D = Death.
Subscript Numerals = Day of death of individual mice.
Numerals = Degree of pulmonary involvement when mice were sacrificed on 10th day.
0 = No pulmonary involvement.

metals and alloys while across the top of the table are shown the species of bacteria and fungi. The variety of responses necessitated the use of a number of symbols, viz:

Partial inhibition of growth	P
Complete inhibition of growth	C
Stimulation of growth	S
Size of zone of diffusion of effect	
No diffusion	D 0
1-10 mm.	D 1
10-20 mm.	D 2
20-30 mm.	D 3
30- mm.	D 4

As an example, reference to the table discloses that antimony partially inhibited the growth of Staphylococcus aureus with a moderate zone of diffusion (PD 2). Complete inhibition of Streptococcus pyogenes, Bacillus subtilis, and Eberthella typhosa is noted (CD 2). The growth of Escherichia coli was partially inhibited with a narrow zone of diffusion (PD 1). Pseudomonas aeruginosa was inhibited completely (CPD 2) immediately around the metal with a partial inhibition zone extending beyond. Complete inhibition of Streptomyces griseus and Streptomyces sp: with excellent diffusion (CD 4) was observed. Stimulation of various organisms was not observed with this metal but is designated by the letter S in the table.

Several metals caused definite changes to appear in the media. Among these were zinc, cobalt, iron, and steel. Surrounding the pieces of iron and steel, oxidized or rust-like material appeared in a few hours.

Our studies of the oligodynamic action of metals on various micro-organisms have served to confirm earlier investigations in this field and will not be analyzed in detail in this paper. For the effect of each metal on the various organisms, the table may be consulted. A zone of inhibition developed when various metallic elements were placed on the surface of a fresh agar plate uniformly inoculated with a young bacterial culture apparently due to slight dissolution of the metal into the culture medium.

Effects of various metals and alloys on virus: Several metals caused a precipitate to form in the virus-suspensions. The precipitated material was thoroughly mixed with the supernatant before inoculation of the suspension into eggs or mice. No acute manifestations were observed when the treated suspensions were given intranasally, though virus suspension which had been in contact with metallic copper longer than 30 min. produced severe reactions when given intracerebrally to mice.

Effects on influenza virus: Several metallic elements and metal alloys were found to have an oligodynamic action on the PR8 strain of influenza virus when tested by mouse inoculation (Table V). No definite effect was observed when virus was in contact with copper (periodic group I) filings for 35 min. Contact with brass which contained 70% copper and 30% zinc seemed completely to inactivate the virus in three hours while the virus activity was greatly reduced after 1½ hours' contact with the metal.

Metallic zinc (periodic group II) was observed to inactivate the virus partially, whereas cadmium and mercury had little or no effect. Zinc powder may have reduced the virus activity approximately 50% in a group of 25 mice. The first deaths in the treated group occurred after approximately half the control animals had succumbed.

The change of pH in the suspensions caused by the presence of magnesium might account for some of the inactivation with this metal.

The two elements in periodic group III selected for test were yttrium, obtainable only in oxide form, and indium. Both of these materials appeared partially to inactivate influenza A virus. Titanium and zirconium of group IV seemed to reduce infectivity of the virus although the pH change caused by titanium might account for some destruction of the virus. Zirconium was observed to destroy sufficient virus so that 18 of 25 animals survived and were found free from infection when sacrificed ten days after inoculation; whereas, of the controls only two survived without evidence of infection.

Of the four elements selected from periodic group V, only tantalum appeared to reduce the infectivity of the virus.

Selenium, tellurium, and tungsten of the elements from periodic group VI apparently destroyed significant amounts of the virus during the one to three hour neutralizing periods.

Manganese and rhenium of periodic group VII elements seemed definitely to inactivate the virus of influenza. Rhenium completely inactivated or removed the virus from the supernatant in one and three hour holding periods. In a larger group of 20 mice a similar destruction or removal from solution was observed. In a later experiment in which adult mice were used and the infecting dose was increased from 0.05 to 0.1 Ml., a 75% survival was observed.

Five elements of periodic group VIII were tested for virucidal activity. Iron in two of three tests was observed to have only a slight effect on the virus while a closely related steel had no apparent effect. Ruthenium, palladium, and iridium had no apparent effect on the virus in suspension. Osmium completely removed or destroyed the virus in the initial test and in a larger scale retest. However, when adult animals and a larger infecting dose of virus suspension were employed removal or inactivation of virus was only partial.

The oligodynamic action of selected metallic elements and metal alloys on influenza A virus when survival of virus was tested by inoculation into the chick embryo is shown in Table VI. Of the 16 metals used, copper, yttrium oxide, columbium, selenium, tungsten, rhenium, osmium, iridium, and brass were observed to destroy or to remove the virus partially from the suspension. Experiments with tungsten and rhenium were repeated with continued evidence of an effect of the metal on the virus.

Table VII summarizes the tests for oligodynamic action of several elements and alloys on the virus of poliomyelitis. The animals receiving the treated and untreated virus suspensions were observed for 30 days before being discarded. Copper caused a definite precipitate to form in virus suspension, and the treated suspension caused severe reactions and death in mice if the period of contact of virus with copper was extended beyond one hour. Copper in lesser periods of contact gave indication of some effect on the virus. Rhenium was the only metal which could be clearly defined as partially removing or destroying the virus. Using powdered rhenium recovered from the initial test and increasing the number of mice to 25, a period of one to three hours' contact with the metal caused no inactivation of the virus. In the next three experiments with fresh rhenium and 25 mice in each group, a partial inactivation was observed. Severe toxic reactions were observed in the first series of mice receiving the treated suspension with 14 of 25 animals dying within 24 hours. None of the remaining animals

TABLE VI

METAL NEUTRALIZATION TESTED BY INOCULATION OF CHICK EMBRYO INFLUENZA A

Group	Metal	Time	Treated			Untreated			Remarks
		Hours*	A	B	C	A	B	C	
I	Copper	½	4	1	85	4	4	0	
II	Zinc	2½	6	4	33	6	4	33	
III	Yttrium	3	4	1	75	4	4	0	Oxide
	Indium	3	4	3	25	4	4	0	
IV									
V	Columbium	3	5	2	60	4	4	0	
		3	15	9	42	6	4	33	
	Bismuth	½	4	4	0	5	5	0	
		3	5	4	20	4	4	0	
VI	Chromium	3	6	6	0	6	6	0	
	Selenium	1	4	4	0	4	4	0	
		2½	6	3	50	6	4	33	
	Tellurium	3	4	4	0	4	4	0	
	Tungsten	2	5	0	100	4	4	0	
		2	24	9	65	6	6	0	
VII	Rhenium	1	4	4	0	4	4	0	2 alive when all controls dead
		3	4	4	0	4	4	0	3 alive when all controls dead
		2	21	7	66	10	8	20	
		3	20	2	90	5	5	0	2 deaths after controls dead
VIII	Osmium	1	4	0	100	4	4	0	
		1	10	10	0	6	6	0	
	Iridium	3	6	3	50	6	6	0	
	Iron	½	4	3	25	5	5	0	Powder reduced by Hydrogen
		3	4	3	25	4	4	0	Powder reduced by Hydrogen
		½	4	3	25	5	5	0	Powder Grade MPDB
		½	4	4	0	5	5	0	Powder Type 14B Hydrogen reduced
	Brass	½	4	2	50	4	4	0	70/30
		1	3	0	100	4	4	0	70/30
	Steel	3	6	5	16	6	6	0	Stainless

Legend: A—Number of eggs used
B—Number of embryos dying
C—Percent of embryos surviving
70/30 Brass—70% copper & 30% zinc
*Incubation period

died or developed paralysis during the 30 day observation period while all control animals in this group succumbed to the infection. This was repeated with a sample of the same lot of rhenium previously used. No toxic reactions followed inoculation of the treated suspension in the succeeding groups, and survival rate was approximately the same as in the preceding experiment. A longer neutralizing period was used in the third

experiment of this series. The time was increased from three to 18 hours with the material left in the cold room (8°C.) instead of at room temperature. The survival rate was not as high as in the previous experiment. However, the mice in the control group had all succumbed to the infection with the exception of one animal before any paralysis was observed in the treated group.

Discussion

There appeared to be some correlation of the oligodynamic activity on micro-organisms of metallic elements as they appear in groups in the periodic table. Gold in group I and

TABLE VII

Metal-Virus Neutralization—Mouse Poliomyelitis

Group	Metal or Element	pH of Metal-Virus Suspension	Mice Inoculated with Virus Exposed to Metal				Control Mice				Remarks
			#	P	D	% Sur.	#	P	D	% Sur.	
I	Copper	7.0[1]	10	0	10	0	10	5	2	30	Toxic—1 hr. exposure—Solid
			10	2	2	60	10	5	4	10	H_2O—½ hr. exposure
		8.35[2]	10	3	3	40	10	5	5	0	NaCl (0.9%)—½ hr. Diarrhea 2 deaths, treated
			10	5	2	30	10	3	4	30	
			25	3	13	32	25	10	2	52	H_2O—½ hr.—Filings
	Silver	7.3[2]	10	2	7	10	10	5	2	30	
II	Magnesium	10.0[1,2]	8	0	6	24	8	6	0	24	Strip NaCl (0.9%)
			8	8	0	0	8	6	0	24	Strip H_2O
			8	8	0	0	8	6	0	24	Powdered NaCl (0.9%)
			8	6	0	24	8	6	0	24	Powdered H_2O
	Zinc	7.0[1]	10	5	3	20	10	5	4	10	Solid
		9.45[2]	10	6	1	30	10	3	4	30	Powdered NaCl
			10	6	4	0	10	5	4	10	Powdered H_2O
	Cadmium	8.5[2]	10	0	9	10	10	5	2	30	Toxic—3 hr.
			10	4	6	0	10	5	4	10	NaCl—1 hr.
			10	5	0	50	10	3	4	30	NaCl—1 hr.
			25	12	9	16	25	10	12	52	H_2O—2 hr.
	Mercury	7.0[1]	10	8	2	20	10	5	2	30	
		8.1[2]	10	9	1	0	10	5	5	0	NaCl
			10	8	2	0	10	5	4	10	H_2O
III	Aluminum	7.75[2]	10	6	0	40	10	3	4	30	Solid
			8	3	5	0	10	6	0	24	
	Gallium		11	5	5	9	25	19	4	8	
IV	Titanium	12.0[1,2]	6	6	0	0	6	5	1	0	Treated 4 deaths toxic
	Zirconium	6.0[1]	6	3	1	32	6	5	1	0	
		7.5[2]									
V	Antimony	6.98[2]	10	5	4	10	10	5	2	30	
	Tantalum	10.0[1]	6	5	1	0	6	5	1	0	
		9.2[2]									
	Bismuth	6.2[1]	6	0	4	32	6	5	1	0	
		7.3[2]									

TABLE VII—(*continued*)

Group	Metal or Element	pH of Metal-Virus Suspension	Mice Inoculated with Virus Exposed to Metal				Control Mice				Remarks
			#	P	D	% Sur.	#	P	D	% Sur.	
VI	Chromium	8.3[1] 8.2[2]	6	3	3	0	6	5	1	0	
	Tellurium	4.8[1] 7.0[2]	6	1	3	32	6	5	1	0	
	Tungsten		6	0	6	0	6	5	1	0	
VII	Manganese	8.7[1] 10.0[2]	6	0	5	16	6	5	1	0	
	Rhenium	6.4[1]	6	0	1	84	6	5	1	0	Death in treated group—28 days
		7.7[2]	22	20	1	5	22	21	0	5	Previously used metal—1 hr. incubation
			25	22	1	8	25	21	2	16	Previously used metal—18 hr. incubation
			25	0	14	44	25	22	3	0	Deaths in treated group—toxic in 48 hr.
			25	5	9	44	25	17	3	16	3 hr.—new metal
			25	10	7	32	25	24	1	0	18 hr. incubation
VIII	Iron	7.5[1] 7.4[2]	12	1	6	40	6	5	1	0	Powder reduced by hydrogen
	Cobalt	8.2[2]	10	5	0	50	10	3	4	30	
			8	3	5	0	8	6	0	24	NaCl (0.9%)
	Palladium	7.5[1] 8.5[2]	6	2	4	0	6	5	1	0	
	Osmium	6.85[1] 7.8[2]	6	1	5	0	6	5	1	0	
	Iridium	9.0[1] 8.2[2]	6	1	3	32	6	5	1	0	
	Brass	7.0[1]	10	0	9	10	10	5	2	30	85/15 Toxic 3 hr. incubation
		8.3[2]	10	5	5	0	10	5	5	0	85/15 1 hr. incubation H_2O
			10	4	3	30	10	3	4	30	85/15 1 hr. incubation NaCl
			10	0	4	60	10	5	2	30	70/30 3 hr. incubation
			10	7	3	0	10	5	4	10	70/30 1 hr. incubation
	Steel	6.1[1]									
		7.3[2]	10	7	3	0	10	5	2	30	S.A.E. 4140
			32	11	18	9	33	7	23	9	S.A.E. 4140 Several deaths in each group due to diarrhea
	Amalgom	7.0[1] 8.0[2]	6	0	6	0	6	5	1	0	Dental

Legend: 1 Distilled water
2 0.9% NaCl
Number of mice in each group
P Paralysis in one or more extremities
D Death without paralysis of extremities
% Sur. Percent survival

cobalt in group VIII were exceptions. Copper and silver of group I were active against many of the representative types of organisms while gold was without apparent effect. Cobalt in group VIII was active against most of the micro-organisms while the other metal-elements in this group were only active against an occasional species.

The action of the elements against the micro-organisms showed a fair but not pronounced correlation when placed in series in the periodic arrangement. The exceptions to this were the presence of one or two elements that showed no effect in series with several very active ones.

Iron and steel produced definite growth changes, inhibition or stimulation, possibly by their ease in oxidizing in liquid media. Stainless steel in both solid and powdered forms was observed to stimulate several micro-organisms to increased growth. No attempts have been made to ascertain how anaerobic conditions might affect oligodynamic action. Buschke, Jacobsohn, and Klopstock[7] found that the oligodynamic action of thallium on micro-organisms was reduced when air was excluded.

Several metals placed in contact with influenza A virus in suspension, partially inactivated the virus or removed it by adsorption to the metal particles.

The apparent oligodynamic activity of the metals against mouse-adapted influenza A virus did not follow the periodic arrangement in groups but showed some correlation when the elements were placed in series. This was best observed in the action of tantalum, tungsten, rhenium, osmium, and iridium.

The results following injection of metal-treated virus suspensions into the chick embryo failed to correlate in several instances with the results obtained using similarly treated suspensions in mice. When inoculated mice were used in tests for survival of virus following contact of virus suspensions with metals, significant effects in destruction or reduction of infectivity of influenza virus was brought about by brass, osmium and rhenium. Lesser but noticeable effects were caused by zirconium, zinc, copper, iridium, yttrium, tantalum, selenium, tellurium, tungsten, and manganese. Rhenium, copper, and brass (70/30) exhibited action against the influenza A virus when presence of virus was tested by either method.

Only one element, rhenium, was observed to exert a definite effect on the virus of poliomyelitis. Partial inactivation followed contact of virus with fresh metallic rhenium powder.

Many of the metals and alloys caused a change in pH of the solutions in which they were suspended. In several cases pH change may have been sufficient to inactivate the virus of influenza and was taken into account in interpreting the results. Change in pH did not appear to affect greatly the virus of poliomyelitis.

Of interest to the authors was also the stimulatory effect on various micro-organisms of certain metallic elements and compounds.

References

1. von Nägeli, Concerning oligodynamic metal effect in bacteria, Denkschr. Schweizer, Naturforsch. Ges. **33**:1, 1893.
2. Albert, A., Falk, J. E., and Rubbo, S. D., Antibacterial action of arsenic, Nature, London. **153**: 712, 1944.
3. Herrero, F. J., Action of cations on growth of bacteria, new method of study, Arch. Farm. Bioquim. Tuchman. **2**:239, 1945.
4. Goetz, A., Self sterilizing coating inhibits bacterial growth, Can. Paint and Varnish Mg. **19**: 12, 1945.

5. Goetz, A., Tracy, R., and Gaetz, S., Self sterilizing surfaces, Science **95**:537, 1942.
6. Petherick, M. H., and Singer, E. V., Action of metals on bacterial intoxication, Australian J. Exper. Biol. and Med. Sci. **22**:21, 1944.
7. Buschke, Jacobsohn, and Klopstock, E., Oligodynamic antibacterial action of metals, Deutsche medizinische Wochenschrift, Berlin. **51**:595, 1925.
8. Braun, M., and Braun, H., Importance of Cu in biology, Süddeut Apoth. Ztg. **82**:326, 1942.
9. Hirsch, K. Z., Copper resistance of spirochetes of Weil types and experiments on isolation of water spirochetes on copper medium, Z. Immunitäts. **71**:459, 1931.
10. Stolmakova, A. I., and Kolonii, V. P., Biological method for qualitative determination of oligodynamic activity of silver waters, Zhur. Mikrobiol. Epidemiol. Immunobiol. **5-6**:125, 1942.
11. Bodine, J. H., and Takmessian, T. N., Effect of heavy metals on activation and injury of enzyme tryrosinase, Arch. Biochem. **2**:403, 1943.
12. Reif, G., Action of metals and metal salts on vitamin C content of milk, Milchw. Forsch. **21**:1, 1941.
13. Nguyen-van-Thoai, and Roche, J., Affinity of proteins for metals and distinction between lyoenzyme and desmoenzyme, Compt. Rend. Soc. Biol. **137**:767, 1943.
14. Ornstein, O., Experimental contributions to oligodynamic action with special references to water purification, Acta Path. Microbiol. Scand. **20**:86, 1943.
15. Saruta, N., and Kitahara K., Temperature reduction of drinking water in stone pots treated with powder and its oligodynamic action, Hukuoka Acta Med. **34**:93, 1941.
16. Sanguineti, A. A., Nature of ascorbic acid in tomato juice after oligodynamic sterilization, Rev. Soc. Argentina Biol. **16**:209, 1940.
17. Warcollier, G., and Tavernier, J., Use of metals in cider industry, inconel, a nickel alloy, Bull. Assoc. Chim. **59**:464, 1942.
18. Hausam, W., Hide preservation with zinc salts, Boll. Staz. Sper. Ind. Pelli. Mat. Concianti Napoli-Torino **19**:55, 1941.
19. Bertuzzi, A., Biophysical or biochemical remote action of metals and prospect for application of "atomoligodynamism" of metals, Chim. Ind. Agr. Biol. **18**:12, 1942.
20. Regnier, J., and Lory, R., Action at distance of heavy metals and cell division (mitogenetic radiation) on growth of micro-organisms, Bull. Assoc. Diplomes Microbiol. Faculte Pharm., Nancy. **24-25**:13, 1942.
21. Bertuzzi, A., Habitation of infusorian olstrichi or colpoda to specific metal vapors, Soc. Ital. Progresso Sci. **27**:239, 1939.
22. Schmidt, W., Physiological action of metals at distance, Ber. Dent. Botan. Ges. **61**:75, 1943.
23. Roffo, A. E., Biological action of metals at distance, Biol. Inst. Exptl. Estud. Cancer. **16**:55, 1939.
24. Schinz, H. R., and Vehlinger, E. Z., Metal cancer; new principle of cancer production, Krebsforsch. **52**:425, 1942.
25. Schultz, E. W., Chemical agents in prevention and treatment of experimental poliomyelitis, Am. J. Pub. Health **30**:175, 1940.
26. Kramer, S. D., Geer, H. A., and Szobel, D. A., Chemoprophylactic and therapeutic action of wide variety of chemical compounds on two neurotropic virus infections in mice, J. Immunol. **49**:273, 1944.
27. Schultz, E. W., and Robinson, F., In vitro resistance of poliomyelitis virus to chemical agents, J. Infect. Dis. **70**:193, 1942.
28. Howitt, B. F., Poliomyelitis virus; results of treating with certain chemicals and with heat, Proc. Soc. Exper. Biol. & Med. **28**:158, 1930.
29. Jungeblut, C. W., Attempts at chemotherapy in experimental poliomyelitis, Proc. Soc. Exper. Biol. & Med. **28**:176, 1930.
30. Contat, C., and Spycher, C., Chlorate de potasse et essais chimiotherapiques in vitro et in vivo de la poliomyelite experimentale du singe, Schweiz. Med. Wchnschr. **69**:719, 1939.
31. Hornus, G., and Haber, P., Etude de l'action de divers corps chimiques sur le virus poliomylitique in vivo et in vitro, Compt. Rend. Soc. de Biol. **117**:656, 1934.
32. Knight, C. A., and Stanley, W. M., Effect of some chemicals on purified influenza virus, J. Exper. Med. **79**:291, 1944.

33. Knight, C. A., Stability of influenza virus (stability of influenza virus in the presence of salts), J. Exper. Med. **79**:285, 1944.
34. Stock, C. C., and Francis, T., Inactivation of virus of epidemic influenza by soaps, J. Exper. Med. **71**:661, 1940.

SPANISH ABSTRACT

Acción Oligodinamica de los Elementos Metálicos y de las Aleaciones Metálicas Sobre Ciertas Bacterias y Virus: I. Observaciones in Vitro

Una reinvestigación de los efectos inhibitorios de los elementos metálicos sobre las bacterias y hongos, confirma y extiende anteriores investigaciones en este campo. Estudios adicionales sobre el virus de la influenza indican marcados efectos en la destrucción o reducción de la infectividad de los virus puestos en contacto con bronce, osmio y rhenio, con un efecto menor ejercido por otros metales Solamente un elemento, el rhenio, puede interpretarse de tener algún efecto sobre el virus poliomielitico.

2065 Adelbert Road

THE RESPONSE OF YOUNG INFANTS TO INGESTION OF AMMONIUM CHLORIDE

By HARRY H. GORDON, M.D., HELEN MCNAMARA, M.A., AND HELEN R. BENJAMIN, PH.D.
Denver, Colo., and New York, N.Y.

IT HAS been reported that prematurely born and full term infants are prone to develop chemical signs of acidosis.[1-10] The greater incidence of salicylate intoxication in young infants,[11] the occurrence of acidosis in premature infants fed protein milk containing relatively large amounts of chloride,[12] the finding of hyperelectrolytemia and hyperchloremia, and of post-acidotic disturbances in serum concentrations of calcium, potassium and phosphate particularly in young infants,[13,14,15] all point to some defect or defects in homeostasis. The increasing evidence[16-32] of renal disability in young full term and premature infants points to one faulty mechanism of control of internal milieu which may be responsible for the disturbances noted.

In the present study, ammonium chloride was fed to three prematurely born and three full term infants in comparable dosage, and observations were made of the ability of the kidneys to produce ammonia and conserve sodium. The two smallest infants in the series became listless, nursed sluggishly, and developed depressed fontanelles and diminished elasticity of the skin, thus confirming the increased susceptibility of smaller infants to acid intoxication. This could not be correlated, however, with differences in renal response, in serum CO_2 content, or in chlorides.

METHODS

The plan of study was essentially that used by Gamble, Blackfan and Hamilton[33] in their observations on the diuretic action of acid-producing salts.

Subjects: Three prematurely born and three full term infants were studied for periods of eight or nine days each.* The prematures were 11, 15 and 45 days old and weighed 2.0, 2.3 and 2.8 kg. at the beginning of observations. The full term infants were 51, 100 and 122 days of age and weighed 3.7, 4.6 and 5.8 kg. at the beginning of observations. The full term infants were "hospital normals" who had apparently recovered from the illnesses for which they had been admitted.

Diets: All the premature and two of the full term infants received diets of powdered, partially skimmed cow's milk; one full term infant received evaporated milk. The preparations of cow's milk were diluted with water and fortified with dextri-maltose to give average dietary intakes of calories, protein and fluid ranging from 122 to 138, 4.5 to 5.6 gm., and 155 to 193 cc./kg. respectively. All the infants received 10 or 20 drops daily of a vitamin A and D concentrate (percomorph oil) and 25 or 50 mg. ascorbic

From the New York Hospital and the Departments of Pediatrics of Cornell University Medical College and the University of Colorado Medical Center.

Presented in part at the Annual Meeting of the Society for Pediatric Research, Atlantic City, N.J., May 4, 1948.

(Received for publication May 19, 1948.)

* The observations which are the basis of this report were made at the New York Hospital in 1941-1942 with the assistance of the United States Children's Bureau.

acid daily. The infants took their feedings well throughout the study with the exceptions of full term infant, D. F., who vomited a small fraction of his total feeding, and premature infants S. L. and M. R. who became very sluggish after 2½ and three days of ammonium chloride ingestion, respectively. For infant M. R. several feedings were given by gavage.

Experimental Procedure: Following foreperiods of constant diet of three to five days, the urine was collected under oil for periods of approximately 24 hours. Each day a freshly boiled collecting set[34] consisting of glass specimen tube, rubber tubing, separatory funnel, and flask was used. As each specimen was passed it was collected under oil and toluol in a flask which was kept in a refrigerator during the 24 hours. These precautions were taken to minimize bacterial formation of ammonia after voiding of the specimens; the relative constancy of the results in the periods before acid administration (Tables I and II) indicate some measure of success.

After two or three days of collection of urine, ammonium chloride in an approximately 10% solution was given to each infant for three days in divided doses with his feedings. The amount given the first infant studied (A. H.) was 0.82 gm./day, a dose within the therapeutic range for infantile tetany. Comparable doses per square meter of surface area (4.84 gm. or approximately 80 mEq.) were then given the other infants. Urine was collected during the three days of ammonium chloride administration and for two to four days thereafter. Feces were collected for one full term and two premature infants, carmine being used as an indicator for separating the experimental periods.

The infants resided in a constant temperature and humidity room throughout observations but no attempt was made to measure the loss of electrolytes through the skin. The observations were not planned as balance studies of the type devised by Levine[35] for use in determining water and energy exchange, but rather as studies in which the administration of a large dose of ammonium chloride could be expected to call forth urinary changes of a magnitude not to be affected significantly by spontaneous variations in excretion through the skin by infants kept in a constant temperature and humidity room.

Chemical Methods: Urine was analyzed daily in duplicate for ammonia,[36] chloride,[37, 38] sodium,[39, 40] and potassium.[41] The macro-Kjeldahl method was used for nitrogen, and phosphorus was determined according to the method of Fiske and Subbarrow[42] with the use of an Evelyn photo-electric colorimeter.

A glass electrode was used in the analyses of pH, titratable acidity and organic acids. The urine was titrated to pH 7.38 for titratable acidity, and from pH 8 to 2.7 for organic acids, after removal of phosphates.[43] No correction was made for creatine and creatinine.

Methods for Feces: The feces were dry ashed (450°C.) and the ash solution analyzed by the same methods used for urine; chlorides, however, were determined directly on the dried powdered feces.

Serum determinations of CO_2 content,[44] chloride,[37, 38] and protein[45] were made at least once during the foreperiod, at the end of the period of acid ingestion, and again several days later. Red cell volume[46] was determined when blood was available.

Measurements of the 24 hour urea clearance[28, 47] of each infant were made usually during the foreperiod.

TABLE I

Effect of Ammonium Chloride on Acid-Base Excretion of Prematurely Born Infants

Subject	Period	Wt. of Infant gm.	Urine		Urine mEq./24 hr.							Urinary N gm./24 hr.	Urea Clearance cc./sq. m./min.	NH_4Cl Ingested mEq./24 hr.	Blood				Remarks
			Vol. cc./24 hr.	pH	Cl	NH_3	Na	K	Titr. ac	Organic Acids	P				Serum CO_2 Content mEq./l.	Serum Cl mEq./l.	Serum Protein gm./100 cc.	Hematocrit %	
A. H.	I.	2760	318	5.6	8.7	3.0	5.5	20.3	5.3	4.1		1.41			25		*4.8		
B.W. 2350 gm.		2740	279	5.5	10.7	3.3	5.1	19.5	6.0	3.8		1.16			27	101	4.2		
Age 15 days																			
S.A. .199 sq. m.																			
	II.	2800	307	4.7	23.9	4.8	14.5	17.6	6.2	4.2		1.45		16.8					
		2780	256	4.7	23.6	6.4	13.3	17.1	6.0	3.2		1.45		14.6	21	124	5.5		
		2810	230	4.8	20.9	8.2	9.2	14.5	5.8	3.3		1.44		14.6	20	117	5.2		No evidence of dehydration
	III.	2840	253	5.1	17.0	10.2	5.1	18.1	6.7	3.4		1.64							
		2880	195	5.1	13.0	8.1	3.6	15.1	6.5	2.2		1.63							
		2940	193	5.3	10.6	5.7	1.7	16.9	7.0	3.6		1.58							
		2920	200	5.6	7.2	4.4	1.5	13.8	6.5	3.5		1.55	21.3		30	100	4.8		
M. R.	I.	2278	154	5.9	12.2	1.4	9.3	10.4	2.5	1.9									
B.W. 2025 gm.		2280	195	5.8	12.6	1.8	6.6	10.5	3.0	2.3	4.8				29		5.1		
Age 11 days		2310	208	5.5	8.4	2.0	4.8	10.5	3.6	2.7	4.4		17.6						
S.A. .172 sq. m.																			
	II.	2310	230	4.9	19.3	4.2	11.5	11.8	4.6	2.8	5.5			13.6					
		2320	238	5.7	22.0	6.2	10.4	13.8	4.5	2.8	5.7			13.6					
		2300	205	5.6	17.2	7.4	6.6	10.3	5.6	2.7	2.9			13.6	21	103	5.4	59.7	Listless. Definite loss of skin elasticity. Ant. fontanelle slightly depressed.
	III.	2340	206	5.5	14.8	7.2	4.0	10.5	5.6	2.6	3.0								Two feedings gavaged, condition improved.
		2320	201	5.1	7.7	4.8	1.6	8.6	4.5	2.2	1.1								
		2320	206	5.8	7.3	4.5	.7	10.7	4.6	2.4	1.3				36	99	4.7	54.7	
															28*		4.5*		
								Feces											
	I.				.07		.08	.09			6.2								
	II.				.14		.02				6.8								
	III.				.10		.02	.10			7.9								
S. L.	I.	2008	178	5.0	5.0	3.2	2.3	9.8	4.9	3.8	5.8								
B.W. 1272 gm.		2040	164	5.1	6.4	3.3	2.4	9.6	5.1	3.1	5.9								
Age 45 days		2060	183	5.3	5.7	2.8	1.2	9.5	4.5	3.7	5.7		11.7		29		5.6	40.9	
S.A. .158 sq. m.																			
	II.	2100	211	4.9	13.5	4.2	5.4	9.3	5.6	3.6	5.1			12.5					
		2140	207	4.8	17.5	5.1	9.3	9.6	6.0	3.8	6.0			12.5	23	112	5.1	39.5	
		2160	204	4.9	18.6	5.7	9.5	9.9	6.0	4.1	6.4			6.3					Moderate loss of skin turgor & elasticity. Ant. fontanelle depressed. Listless. Skin elasticity still impaired. NH_4Cl discontinued after 4 feedings.
	III.	2140	188	4.9	11.3	5.2	5.1	9.0	6.4	5.1	5.0								
		2160	155	5.0	7.3	4.9	2.4	9.8	5.9	4.4	4.3								Fontanelle moderately depressed.
								Feces											
	I.				.01		.01				3.0								
	II.				.05		.02				2.4								

*6th day after cessation of NH_4Cl.

Results

The detailed results are presented in Tables I and II and Figures 1-6, a summary of the serum findings in Table III, and of some of the urinary findings in Figure 7.

Clinical Response to Ingestion of Ammonium Chloride: The only infants who showed clinical evidence of intoxication were the two smallest infants, S. L. and M. R., who weighed 2.1 and 2.3 kg. at the beginning of observations. The former, who was the smallest infant studied, showed considerable listlessness, depression of the fontanelle, and loss of skin elasticity on the second day of acid administration. On the third day, because of persistent dehydration and increasing listlessness, ammonium chloride was discontinued after half the daily dose had been given. The infant's behavior improved in several hours and signs of dehydration disappeared within 24 hours. The other infant who became ill was M. R. After 2½ days of acid administration, he became listless, sucked sluggishly, and showed depression of the fontanelle and loss of elasticity of the skin. Neither the third prematurely born infant nor any of the full term infants showed clinical evidences of dehydration.

Changes in Blood: The measured changes in the blood are summarized in Table III. The changes in serum CO_2 content were of the same magnitude in all six infants, the lowest level of 16 mEq/l. occurring in one of the full term infants. Furthermore, it is seen that serum chlorides in the two infants who became ill were not abnormal, the levels of 103 and 112 mEq/l. being within the range for the three full term infants, 104-111 mEq/l. On the other hand, premature infant, A. H., who showed no evidence of clinical dehydration, did show hemoconcentration as indicated by rises in serum chlorides from 101 to 124 and 117 mEq/l. and in serum protein from an average of 4.5 gm. in the foreperiod to 5.5 and 5.2 gm./100 cc. at the end of two and three days of ammonium chloride administration. Since no correlation could be found between these customary measures of extracellular disturbances and the clinical condition of the two sick infants, one may question the need for additional measurements such as serum pH or other electrolytes. The fact that the two infants gained 30 and 40 gms. (see Table I) respectively during the period when they were becoming clinically dehydrated suggests that internal shifts of fluid were taking place[48,49] and that perhaps measurements of intracellular electrolytes[50,51] would have given a better explanation of the clinical findings.

Electrolyte Excretion: Analyses of the feces were made for one full term and two premature infants. During the period of acid ingestion, none showed significant changes in sodium, potassium, chloride or phosphate excretion (Tables I and II). In the afterperiods, full term infant D. F. showed a moderate increase in sodium excretion (2.2 mEq/24 hr. compared with an average daily urinary excretion of 8.1 mEq). Premature infant M. R. showed a moderate increase in phosphate output (1.7 mEq/24 hr. increase compared with the average daily urinary excretion of 4.6 mEq. during the foreperiod and 1.8 mEq. during the afterperiod).

The 24 hour urea clearances for the three prematurely born and three full term infants were 12, 18 and 21 cc. and 24, 25 and 31 cc./sq.m/min., respectively. These results are in agreement with previous findings.[28]

The detailed daily urinary excretions are presented in Tables I and II. The changes are presented graphically in relation to surface area in Figures 1-6, to facilitate comparison. For each infant, the average excretion of the two or three days of foreperiod

TABLE II

Effect of Ammonium Chloride on Acid-Base Excretion of Full Term Infants

Subject	Period	Wt. of Infant gm.	Urine		Urine mEq./24 hr.							Urinary N gm./24 hr.	Urea Clearance cc./sq. m./min.	NH_4Cl Ingested mEq./24 hr.	Blood				Remarks
			Vol. cc./24 hr.	pH	Cl	NH_3	Na	K	Titr. ac.	Organic Acids	P				Serum CO_2 Content m.Eq./l.	Serum Cl m.Eq./l.	Serum Protein gm./100 cc.	Hematocrit %	
D. H.	I.	5820	275	5.0	22.0	9.7	14.0	32.2	16.3	7.3		2.78							Convalescent, removal of Meckel's diverticulum for hemorrhage. Post-operative bronchopneumonia.
B.W. 2937 gm.		5880	339	5.7	16.6	9.8	12.2	31.9	15.8	7.7		2.61	23.6		27	104	5.9		
Age 122 days																			
S.A. .350 sq. m.																			
	II.	6000	410	5.1	41.7	12.4	27.0	37.2	14.9	8.6		3.02		27.7					
		6060	333	5.0	38.8	16.9	17.2	34.1	17.6	8.1		3.09		27.7					
		5940	314	5.0	41.7	22.8	15.3	35.4	18.0	9.4		3.38		27.7	21	110	5.8		No evidence of dehydration
	III.	5940	294	5.2	28.6	24.8	7.0	29.9	17.7	8.9		3.23							
		6140	430	5.7	22.8	13.4	11.0	38.7	14.2	7.8		2.85							
		6200	329	6.3	23.7	6.3	20.9	35.5	9.7	6.8		2.69			32	106			
		6280	332	6.1	20.3	7.9	16.4	36.5	14.0	7.4		3.14	24.5		32	110	5.7		
D. F.	I.	4580	288	5.0	11.9	9.4	8.1	22.5	14.7		22.7				23	107	5.6	32.9	Convalescent from vomiting of unknown origin, complicated by diarrhea.
B.W. 2937 gm.		4620	320	5.1	11.8	11.9	8.0	25.5	17.1	7.6	26.4		30.6						
Age 100 days		4640	289	5.1	11.7	12.4	7.1	17.2	15.0	5.2	25.3								
S.A. .290 sq. m.																			
	II.	4640	337	5.0	23.4	15.0	12.1	19.4	15.5	6.8	22.9			23.0					Vomited several times.
		4700	359	5.1	31.2	22.1	10.4	22.6	15.3	7.9	22.5			21.4					Vomited several times, no evidence of dehydration.
		4760	243	5.2	23.5	21.0	7.1	17.7	12.6	7.0	19.0			18.1	16	111	5.2	34.5	
	III.	4810	280	5.3	22.2	19.5	8.1	14.9	12.7	6.9	20.6								
		4800	354	5.4	20.6	18.2	8.2	17.2	13.7	7.4	24.6				23	104	4.9	31.5	
					Feces														
	I.				9.9		2.3	5.0			7.9								
	II.				9.1		9.1	11.6			7.6								
	III.				10.1		24.7	14.1			7.1								
D. S.	I.	3740	440	5.7	14.2	3.4	10.0	20.9	10.7	4.8		2.34							Convalescent—diarrhea
B.W. 3087		3800	562	5.8	20.4	4.7	14.5	26.6	9.0	5.7		2.56			29	106	5.1		
Age 51 days																			
S.A. .251 sq. m.																			
	II.	3840	372	4.7	25.6	8.4	12.5	17.8	9.3	5.2		2.35		20.0					
		3880	444	4.6	26.5	14.2	11.1	23.3	12.3	5.9		2.37		20.0					
		4060	395	4.6	29.1	15.9	11.4	22.1	11.3	6.6		2.27		20.0	23	107	5.2		No evidence of dehydration.
	III.	4100	340	4.8	18.9	12.9	6.6	19.5	11.1	5.6		1.94							
		4120	343	4.8	14.7	9.6	3.2	24.3	11.1	5.9		2.02							
		4140	361	5.8	13.8	6.2	6.4	25.6	9.0	5.6		2.03							
		4200	369	6.2	12.2	4.5	10.5	26.1	7.4	6.0		2.12	24.5		33	98	5.0		

is considered the base line,[33] and the extent of deviation is indicated in each day of the foreperiod, of the period of ammonium chloride administration, and of the afterperiod.

Foreperiod: It is seen that in individual infants a certain amount of fluctuation in excretion took place during the foreperiod, but this was not larger for the premature than the full term infants (Figures 1-6). The fact that the infants had received cow's milk for long periods prior to the study, the simplicity of the diet, its administration in six or eight aliquots throughout the 24 hours, the use of a constant temperature and humidity room are factors which may have minimized daily fluctuations.

TABLE III

SUMMARY OF CHANGES IN SERUM CO_2, CHLORIDES, AND PROTEINS

	Premature Infants				Full-Term Infants			
		a	b	change		a	b	change
CO_2	S. L.	29	23*	−6	D. S.	29	23	−6
content	M. R.	29	21*	−8	D. F.	23	16	−7
mEq./l.	A. H.	26	20	−6	D. H.	27	21	−6
Chloride	S. L.		112*		D. S.	106	107	+1
mEq./l.	M. R.		103*		D. F.	107	111	+4
	A. H.	101	124	+19	D. H.	104	110	+6
			117					
Protein	S. L.	5.6	5.1*	−0.5	D. S.	5.1	5.2	+0.1
gm./100 cc.	M. R.	5.1	5.4*	+0.3	D. F.	5.6	5.2	−0.4
	A. H.	4.5	5.3	+0.8	D. H.	5.9	5.8	−0.1

[a] Before administration of ammonium chloride.
[b] After administration of ammonium chloride.
* Clinically dehydrated and listless at time of determination.

Effect of Ingestion of Ammonium Chloride: Following the administration of ammonium chloride, there was a sharp rise in chloride excretion in all infants (Figures 1-6). For the full term infants, the average increase in chloride excretion over the foreperiod level for the four days which included the first day after cessation of medication, ranged from 31 to 53 mEq./sq.m./day (Figure 7), and an average of 75% (range from 51 to 89%) of the ingested dose was excreted. The premature infants excreted an excess of chloride over the foreperiod level of from 42 to 60 mEq./sq.m./day. Contrary to expectations,[12] this represented a higher average percentage of the ingested dose, 98% (range 71 to 121%), than was obtained for the full term infants. Premature infant, H., excreted virtually as much excess chloride in the four days as was ingested, confirming the inference that the elevation of serum chlorides previously noted (Table III) represented hemoconcentration rather than chloride retention.

Excess ammonia for the four day period represented 114, 62 and 51% of the excess chloride excretion for the full term infants and 64, 36 and 21% for the premature infants. For the two premature infants (H. and L.) who showed less ammonia excretion

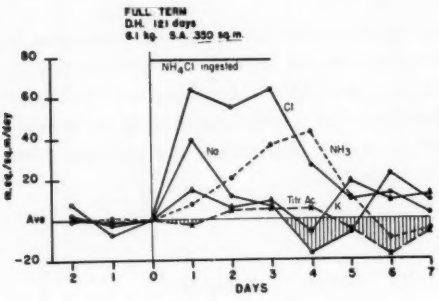


FIG. 1

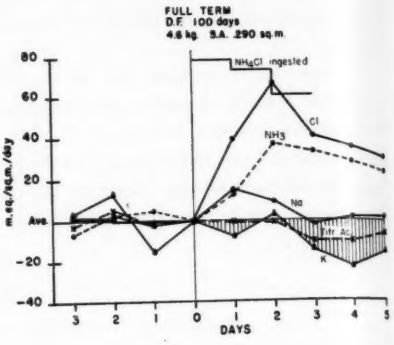


FIG. 2

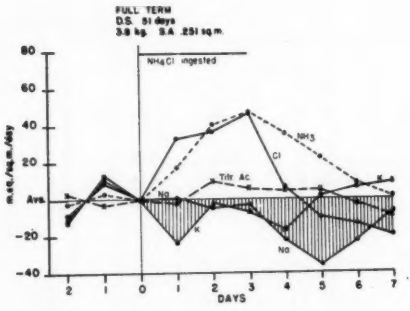


FIG. 3

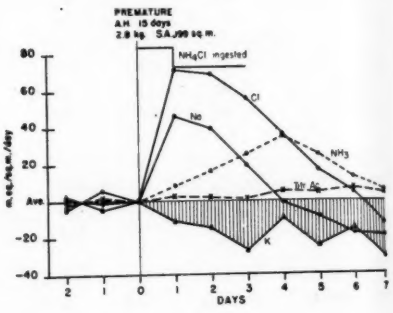


FIG. 4

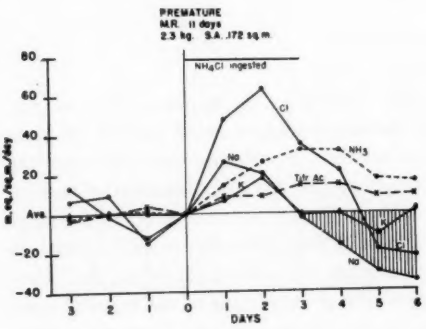


FIG. 5

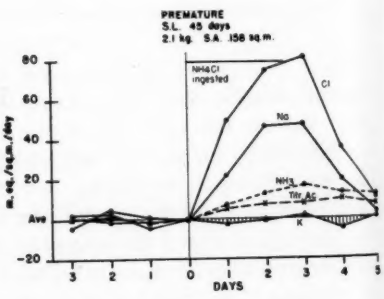


FIG. 6

FIGS. 1-6 (incl.). Effect of ingestion of ammonium chloride on electrolyte excretion of individual infants. Base line marked "Average" is average of foreperiod levels. The areas above and below the base line represent increases and decreases in excretion above and below the foreperiod levels.

than the full term infants, the sodium excretion was conversely greater. The results suggest but do not prove the existence of a diminished ability of the renal tubules of premature infants to produce ammonia and conserve sodium when challenged with excess chloride excretion. Paradoxically, one of the two premature infants who showed diminished ammonia formation, infant H., did not become clinically ill, and one of the two infants who became ill, infant R., showed no diminution in ammonia excretion. Thus, only one infant, L., showed both increased susceptibility to acid intoxication and diminished renal tubular function as evidenced by failure to produce adequate ammonia. One must conclude that renal disability with respect to sodium conservation is not the whole explanation for the suscepibility of small infants to acid intoxication.

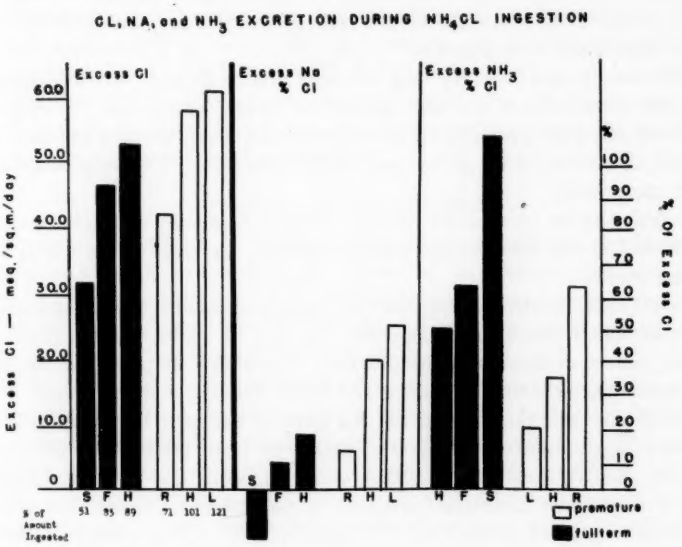


FIG. 7. Summary of results: relation of excess sodium and ammonium excretion to excess chloride excretion. Each column represents average of four days which include three days of ammonium chloride administration and first day of afterperiod.

Potassium excretion showed variable changes in both groups of infants, being either slightly elevated, unchanged, or depressed in both groups of infants during the period of chloride administration. Considerable depressions in potassium excretion were found in full term infant D. S. and premature infant A. H., but their significance cannot be estimated. For the two infants (R. and L.) who became ill there was no consistent change in potassium excretion over the four day period. Infant R. showed a total excess urinary excretion of 4.4 mEq. for the four day period while the excretion in infant L. remained virtually unchanged throughout the period of acid administration.

No striking changes were found in titratable acidity, organic acids or urine volume. The lack of diuresis in the infants with increased sodium excretion may have been due to the fact that more than enough fluid was available at all times for excretion of electrolytes. The avidity of the tissues of these rapidly growing infants for phosphorus[52]

may have limited the amount of the titratable acid response as a mechanism for conserving base.[53-56] In one of the three infants for whom urinary phosphate was determined, infant R., phosphate excretion decreased markedly during the afterperiod, a change similar to that noted by Guest and Rapoport[50, 51] during recovery from acidosis.

Comment

These observations were designed to compare the effect of ingestion of comparable doses of ammonium chloride on the acid-base balance of prematurely born and young full term infants fed similar diets. It was hoped that we could determine, first, whether premature infants were more susceptible to acid intoxication than full term infants, as suggested by the more frequent occurrence of "spontaneous" acidosis in newborn and premature infants; and, second, whether this increased susceptibility, if found, was related to diminished renal function.

The fact that of six infants the only two who became ill were the two smallest ones suggests that these subjects are more susceptible to acid intoxication. In other words, even without assuming some peculiarity in metabolism which permits increased production of acid metabolites, although one may well be present,[9, 10, 57, 58] the premature infants are upset more easily.

The second question concerns the relation of this susceptibility to acid intoxication and the diminished kidney function of premature infants. No clear cut answer is available from these studies.

Studies of maximal tubular excretion by premature infants of p-amino-hippurate[18] show a reduction in excretion as compared with that of adults, and the results of our study also present evidence suggesting a tubular disability in premature infants. The lack of correlation between the urinary and blood findings, and the clinical condition of the two infants who became sick, and the gains in weight in the presence of clinical dehydration, suggest shifts of water and electrolyte from extracellular to vascular or intracellular compartments. The possibility exists that shifts may have been conditioned by a direct intracellular disturbance produced by the absorption of ammonium chloride. Guest[50, 51] has repeatedly pointed out the importance of organic phosphate metabolism in the regulation of intracellular acid base balance; since this must be at least partially dependent on the level of intracellular enzymatic function, one may speculate on the existence of differences in enzymatic function, and in intracellular defense of acid-base balance in the two groups of infants. The present study contains no evidence for or against this conjecture.

What are some of the clinical implications of the various reports which indicate a disability in regulation of acid-base balance in young infants? First, in the young infant as in the nephritic, one may expect any stress—be it diarrhea, vomiting, starvation, improper feeding, or ingestion of toxic substances—to produce greater disturbances of acid-base balance. Second, variations and limitations in adaptability "must always, in certain respects, prevent precision of definition,"[59] i.e., over-simplification or generalizations which have led to controversy about types or quantities of repair solutions. Gamble[60] has written about precise misinformation supplied by metabolic studies and Dr. O. M. Schloss in discussing an infant with pyloric stenosis whose alkalosis had not responded to calculated therapy, once commented: "The trouble may lie in the fact that we are dealing with a funnel rather than a test tube." The problem of therapy thus becomes

a difficult one, to be solved neither by a rigid standardization of amounts and types of repair solutions, nor by a nihilistic approach to metabolic data which do yield first approximations. Rather one must be aware of the need of early diagnosis and early treatment, using frequent clinical and chemical observations both before and during treatment, as guides to individualized care.[61,62] The great benefits derived from the use of normal saline, glucose solutions, and blood need not overshadow the use of the long espoused lactate and lactate-salt solutions,[63] or more recent recommendations for solutions containing sodium chloride in hypotonic amounts and ions aimed at intracellular repair.[64-68] Studies on the life raft ration[69] have shown again[70] the direct relationship between the supply of energy foods and electrolyte losses, and recent observations on alkalosis have indicated the interdependence of serum bicarbonate and intracellular potassium concentrations.[71,72] It becomes obviously desirable to plan programs of repair which meet requirements of energy, protein, vitamins, and predominantly intracellular ions as well as of water and sodium chloride,[73,74,65-68] Finally, there needs to be accurate recording of therapy[75] if one is to give a newborn infant with diarrhea the best possible treatment. Actually, his management is as specialized a performance as the modern treatment of a patient with influenzal meningitis.[76]

Summary and Conclusions

The results of observations of the effect of ingestion of ammonium chloride on the acid-base excretion of three premature and three full term infants are presented. Two of the three premature infants showed a definitely diminished ammonia and increased sodium excretion as compared with the full term infants. The results suggest that some premature infants may have a renal tubular disability.

One of the two infants with diminished ammonia formation and the third premature infant, the two smallest in the series, became listless, refused their feedings, and developed depressed fontanelles and diminished elasticity of the skin. This could not be correlated with changes in serum CO_2 content or chlorides or with the presence or absence of an adequate urinary formation of ammonia and conservation of sodium. Since the infants who became dehydrated gained weight while doing so, shifts of water and electrolytes from extracellular to vascular or intracellular compartments must have occurred. It is suggested that the tendency of young infants to disturbances of acid-base balance may be conditioned by disabilities in intracellular metabolism as well as by renal dysfunction.

The implications of the limitations and variability in homeostasis for therapy are discussed.

References

1. Pfaundler, M., Physikalisch-chemische Untersuchungen am Kinderblut, Verhandl. d. Gesellsch. f. Kinderh., Breslau, 1904, p. 24.
2. Ibid., Jahrb. f. Kinder., **60**:719, 1940.
3. Yllpo, A., Neugeborenen; hunger und Intoxikationsacidosis in ihren Beziehungen zueinander, Ztschr. f. Kinderh. **14**:268, 1916.
4. Yllpo, A., Beitrag zur Azidosis bei Neugeborenen, Acta Paediat. **3**:235, 1924.
5. Hoag, L. A., and Kiser, W. H., Jr., Acid-base equilibrium of newborn infants; normal standards, Am. J. Dis. Child. **41**:1054, 1931.
6. Marples, E., and Lippard, V. W., Acid-base balance of newborn infants; consideration of low alkaline reserve of normal newborn infants, Am. J. Dis. Child. **44**:31, 1932.

7. Marples, E., and Lippard, V. W., Acid-base balance of newborn infants; influence of cow's milk on acid-base balance of blood of newborn infants, Am. J. Dis. Child. **45**:294, 1933.
8. Lippard, V. W., and Marples, E., Acid-base balance of newborn infants; effect of ingestion of alkali on acid-base balance of newborn infants, Am. J. Dis. Child. **46**:495, 1933.
9. Branning, W. S., Acid-base balance of premature infants, J. Clin. Investigation **21**:101, 1942.
10. McBryde, A., and Branning, W. S., Spontaneous acidosis in premature infants; clinical report, J. Pediat. **20**:549, 1942.
11. Erganian, Jane, Forbes, G. B., and Case, Dorothy M., Salicylate intoxication in infant and young child, J. Pediat. **30**:129, 1947.
12. Darrow, D. C., da Silva, M. M., and Stevenson, S. S., Production of acidosis in premature infants by protein milk, J. Pediat. **27**:43, 1945.
13. Rapoport, S., Discussion before American Pediatric Society, Am. J. Dis. Child. **72**:483, 1946.
14. Rapoport, S., Hyperosmolarity and hyperelectrolytemia in pathologic conditions of childhood, Am. J. Dis. Child. **74**:682, 1947.
15. Rapoport, S., Dodd, Katherine, Clark, M., and Syllm, I., Postacidotic state of infantile diarrhea: symptoms and chemical data, Am. J. Dis. Child. **73**:391, 1947.
16. Barnett, H. L., Renal physiology of infants and children: I. Method for estimation of glomerular filtration rate, Proc. Soc. Exper. Biol. Med. **44**:654, 1940.
17. Barnett, H. L., Perley, Anne M., and McGinnis, H. G., Renal physiology in infants and children. II. Inulin clearances in newborn infant with extrophy of bladder. Proc. Soc. Exper. Biol. Med. **49**:90, 1942.
18. Barnett, H. L., McNamara, Helen, Hare, R. S., and Hare, K., Inulin, urea mannitol and PAH clearance ratios in premature infants, Proc. Fed. Am. Soc. for Exper. Biol., **7**:5, 1948.
19. McCance, R. A., and Young, W. F., Secretion of urine by newborn infants, J. Physiol. **99**:265, 1941.
20. Young, W. F., Hallum, J. L., and McCance, R. A., Secretion of urine by premature infants, Arch. Dis. Childhood **16**:243, 1941.
21. Young, W. F., and McCance, R. A., Secretion of urine by dehydrated and normal infants, Arch. Dis. Childhood **17**:65, 1942.
22. Dean, R. F. A., and McCance, R. A., Inulin, diodone, creatinine and urea clearances in newborn infants, J. Physiol. **106**:431, 1947.
23. Rubin, M. I., Bruck, Erica, and Rapoport, M., Studies of maturation of renal function in normal children and renal functional disturbances during various forms of kidney disease in childhood, Program of Fifth International Congress of Pediatrics, Quart. Rev. Pediat. **2**:524, 1947.
24. Smith, C. A., Renal function in early postnatal life in premature and mature infants, Program of Fifth International Congress of Pediatrics, Quart. Rev. Pediat. **2**:494, 1947.
25. West, J. R., Smith, H. W., and Chasis, H., Methods for measuring renal clearance, with special reference to infancy and childhood, Program of Fifth International Congress of Pediatrics, Quart. Rev. Pediat. **2**:524, 1947.
26. Heller, H., Renal function of newborn infants, J. Physiol. **102**:429, 1944.
27. Gordon, H. H., Harrison, H. E., and McNamara, Helen, Urea clearance of young premature and full term infants, Am. J. Dis. Child. **62**:894, 1941.
28. Ibid., J. Clin. Investigation **21**:499, 1942.
29. Peter, K., Untersuchungen über Bau und Entwicklung der Niere, Vol. I and II, G. Fischer, Jena, 1909-1927.
30. Clara, M., Vergleichende Histobiologie des Nierenglomerulus und der Lungenalveole, Ztschr. f. mikr-anat. Forsch **40**:47, 1936.
31. Gruenwald, P., and Popper, H., Histogenesis and physiology of renal glomerulus in early postnatal life: histological examinations, J. Urol. **43**:452, 1940.
32. Potter, Edith, and Thierstein, S. T., Glomerular development in kidney as index of fetal maturity, J. Pediat. **22**:695, 1943.
33. Gamble, J. L., Blackfan, K. D., and Hamilton, B., Study of diuretic action of acid producing salts, J. Clin. Investigation **1**:359, 1925.
34. Hoag, L. A., Apparatus for quantitative collection of urine and stools in male infants, Am. J. Dis. Child. **44**:770, 1932.

35. Gordon, H. H., Levine, S. Z., Deamer, W. C., and McNamara, Helen, Respiratory metabolism in infancy and childhood, XXIII, Daily energy requirements of premature infants, Am. J. Dis. Child. **59**:1185, 1940.
36. VanSlyke, D. D., and Cullen, G. E., Determination of urea by the urease method, J. Biol. Chem. **24**:117, 1916.
37. VanSlyke, D. D., Determination of chlorides in blood and tissues, J. Biol. Chem. **58**:523, 1923.
38. Eisenman, A. J., Note on VanSlyke method for determination of chlorides in blood and tissue, J. Biol. Chem. **82**:411, 1929.
39. Butler, A. M., and Tuthill, E., An application of the uranyl zinc acetate method for determination of sodium in biological material, J. Biol. Chem. **93**:171, 1931.
40. Barber, H. H., and Kolthoff, I. M., Specific reagent for rapid gravimetric determination of sodium, J. Am. Chem. Soc. **50**:1625, 1928.
41. Harrison, H. E., and Darrow, D. C., Volumetric method for determination of potassium in biological materials, J. Biol. Chem. **121**:631, 1937.
42. Fiske, C. H., and Subbarrow, Y., Colorimetric determination of phosphorus, J. Biol. Chem. **66**:375, 1925.
43. VanSlyke, D. D., and Palmer, W. W., Studies of acidosis; titration of organic acids in urine, J. Biol. Chem. **41**:567, 1920.
44. VanSlyke, D. D., and Neill, J. M., Determination of gases in blood and other solutions by vacuum extraction and manometric measurement, J. Biol. Chem. **61**:523, 1924.
45. Neuhausen, B. S., and Rioch, D. M., Refractometric determination of serum proteins, J. Biol. Chem. **55**:353, 1923.
46. Smith, C. H., Method for determining sedimentation rate and red cell volume in infants and children with use of capillary blood, Am. J. M. Sc. **192**:73, 1936.
47. Van Slyke, D. D., and Kugel, V. H., Improvements in manometric micro-Kjeldahl and blood urea methods, J. Biol. Chem. **102**:489, 1933.
48. Darrow, D. C., and Yannet, H., Changes in distribution of body water and accompanying increase and decrease in extracellular electrolyte, J. Clin. Investigation **14**:266, 1935.
49. Darrow, D. C., and Yannet, H., Metabolic studies of changes in body electrolyte and distribution of body water induced experimentally by deficit of extracellular electrolyte, J. Clin. Investigation **15**:419, 1936.
50. Guest, G. M., and Rapoport, S., Role of acid-soluble phosphorus compounds in red blood cells in experimental rickets, renal insufficiency, pyloric obstruction, gastro-enteritis, ammonium chloride acidosis and diabetic acidosis, Am. J. Dis. Child. **58**:1072, 1939.
51. Guest, G. M., Organic phosphates of blood and mineral metabolism in diabetic acidosis, Am. J. Dis. Child. **64**:401, 1942.
52. Benjamin, H. R., Gordon, H. H., and Marples, E., Calcium and phosphorus requirements of premature infants, Am. J. Dis. Child. **65**:412, 1943.
53. Pitts, R. F., Renal regulation of acid base balance with special reference to mechanism for acidifying urine, Science **102**:49, 81, 1945.
54. Pitts, R. F., and Lotspeich, W. D., Factors governing rate of excretion of titratable acid in dog, Am. J. Physiol. **147**:481, 1946.
55. Pitts, R. F., Lotspeich, W. D., Schiess, W. A., and Ayer, J. L., Renal regulation of acid-base balance in man. I. Nature of mechanism for acidifying urine, J. Clin. Investigation **27**:48, 1948.
56. Schiess, W. A., Ayer, J. L., Lotspeich, W. D., and Pitts, R. F., Renal regulation of acid-base balance in man. II. Factors affecting excretion of titratable acid by normal human subject, J. Clin. Investigation **27**:57, 1948.
57. Seckel, H., and Sommer, W., Harnmilchsäure-Ausscheidung bei Frühgeborenen und Ausgetragenen Säuglingen, Klin. Wchnschr. **14**:1602, 1935.
58. Raïhä, C. E., Säuglingsmortalität und Frühgeburtlichkeit, Acta Paediat. **28**:27, 1940.
59. Henderson, L. J., Theory of neutrality regulation in animal organism, Am. J. Physiol. **21**:427, 1908.
60. Gamble, J. L., General terms of food requirement, Brennemann's Practice of Pediatrics, Vol. I., Chapt. 23, W. F. Prior, Hagerstown, Md., 1944.
61. Darrow, D. C., Disturbances in electrolyte metabolism in man and their management, Bull. New York Academy Med. **24**:147, 1948.

62. Hartmann, A. F., and Erganian, Jane, Treatment of diabetic acidosis, J. Pediat. **31**:274, 1947.
63. Hartmann, A. F., and Senn, M. J. E., Studies in metabolism of sodium r-lactate; response of human subjects with acidosis to intravenous injection of sodium r-lactate, J. Clin. Investigation **11**:337, 1932.
64. Aldridge, A. G. V., Comparison of value of crystalloid solutions, whole blood and plasma in treatment of dehydration in infancy, Arch. Dis. Child. **16**:182, 1941.
65. Darrow, D. C., Retention of electrolyte during recovery from severe dehydration due to diarrhea, J. Pediat. **28**:515, 1946.
66. Govan, C. D., Jr., and Darrow, D. C., Use of potassium chloride in treatment of diarrhea in infants, J. Pediat. **28**:541, 1946.
67. Darrow, D. C., Advances in treatment of diarrhea in infants, Texas Reports on Biology and Medicine **5**:29, 1947.
68. Butler, A. M., Talbot, N. B., Crawford, J. L., MacLachlan, E. A., and Appleton, J., Parenteral fluid therapy in diarrheal disease, Am. J. Dis. Child. **72**:481, 1946.
69. Butler, A. M., Gamble, J. L., Talbot, N. B., MacLachlan, E. A., Appleton, J., Fahey, Kathleen, and Linton, M. A., Jr. Studies on life raft ration, Quoted by Gamble, J. L., and Wallace, W. McL. Program of Fifth International Congress of Pediatrics, Quart. Rev. Pediat. 2:506, 1947.
70. Gamble, J. L., Ross, S. G., and Tisdall, F. F., Metabolism of fixed base during fasting, J. Biol. Chem. **57**:633, 1923.
71. Darrow, D. C., Changes in muscle composition in alkalosis, J. Clin. Investigation **25**:324, 1946.
72. Darrow, D. C., Schwartz, R., Lannucci, J. F., and Coville, F., Relation of serum bicarbonate concentration to muscle composition, J. Clin. Investigation **27**:198, 1948.
73. Butler, A. M., and Talbot, N. B., Parenteral fluid therapy; estimation and provision of daily maintenance requirements, New England J. Med. **231**:585, 1944.
74. Butler, A. M., and Talbot, N. B., Parenteral fluid therapy; estimation of losses incident to starvation and dehydration with acidosis or alkalosis and provision of repair therapy. New England J. Med. **231**:621, 1944.
75. Dodd, Katherine, and Rapoport, S., Intravenous alimentation of infants, J. Pediat. **69**:758, 1946.
76. Alexander, Hattie E., Treatment of purulent meningitides, Advances in Pediatrics, Vol. II., Interscience Publishers, Inc., New York, 1947.

SPANISH ABSTRACT

La Respuesta de los Niños a la Ingestion de Cloruro Amonico

Se presentan los resultados de observaciones del efecto de la ingestión de cloruo amónico sobre la excreción aciso base de tres prematuros y tres niños a término. Dos de los tres niños prematuros demostraron una marcada disminución de la excreción amómica y aumento de la excreción sodica, comparado con los tres niños a término. Los resultados sugieren que algunos de los niños prematuros pueden tener un transtorno tubular renal.

Uno de los dos niños con disminución de la producción amónica y el tercer niño prematuro, los dos mas pequeños de la série, se volvieron indiferentes, rehusaron los alimentos, y sus fontanelas se hicieron depresibles y disminuyó la elasticidad de la piel. Esto no pudo relacionarse con cambios en el contenido de CO_2 en el suero, cloruros o con la presencia o ausencia de una adecuada formación de amoníaco y conservación del sodio. Ya que los niños, que estaban deshidratados, ganaron peso tratados asi, deben ocurrir cambios de agua y electrolitos desde los compartimentos extracelulares a los vasculares o intracelulares. Se sugiere que la tendencia de los niños pequeños a transtornos del balance acido base, puede ser condicionada por transtornos en el metabolismo intracelular, asi como por disfunción renal.

Se discuten las implicaciones de las limitaciones y variabilidad en homeostasis para la terapeutica.

4200 E. Ninth Ave.

FLUORESCEIN CIRCULATION TIMES IN DIPHTHERIA

By SIDNEY COBB, M.D., AND HORACE L. HODES, M.D.
Ayer, Mass., and Baltimore, Md.

EVALUATION of diphtheritic myocarditis has never been easy. The purpose of this report is to show that measurement of the circulation time can be helpful in dealing with this problem. Since all the patients in this series who showed signs of circulatory inefficiency had evidence of myocarditis, no attempt will be made to distinguish between cardiac failure and peripheral collapse though in some instances these two problems appeared to co-exist as will be seen from the case reports.

METHOD

At the suggestion of Dr. Robert F. Ziegler, the method of Lange and Boyd[1] (1942) and Witzberger and Cohen[2] (1943) was adapted to our purpose. The fluorescein technic was selected because it gives an objective end point which is essential in dealing with infants and small children and yet is free of the dangers associated with cyanide or radioactive materials. Five percent sodium fluorescein* is injected as rapidly as possible (1 to 2.5 seconds) through a #20 needle into one of the antecubital veins. The end point is observed in the lips or palpebral conjunctiva in a darkened room under ultraviolet light.† The time is recorded to the nearest half second from a stop watch which is started at the beginning of the injection. The dose of fluorescein is varied according to weight. Two cc. are given to all patients under 18 kg. in weight. For each additional 14 kg. body weight, the dose is increased by 1 cc. When the dose is 5 cc. or more, it is better given through a #18 needle in order to keep the injection time under 2.5 sec. Patients with prolonged times usually need much larger doses. It has been the authors' policy to grade all end points excellent, good, fair or poor, and it has been found that fair and poor end points give distinctly longer times than the excellent and good ones. Only excellent and good end points are accepted for record. The procedure can ordinarily be repeated in about 20 minutes when the peak of skin fluorescence has passed. Patients with urinary suppression and/or edema may retain the dye in the skin for several days. Dr. Ziegler is at present engaged in a more detailed study of the problems of technic in children.

NORMAL VALUES

A group of patients with various conditions not related to the cardiovascular system were studied at various Baltimore hospitals.‡ The results appear in Figure 1.

The solid line, which represents the upper limit of normal, was drawn by inspection in such a fashion that less than 5% of the values lie to the right of it. There is only

From Sydenham Hospital and Department of Preventive Medicine, Johns Hopkins Medical School, Baltimore, Md.

* Fluorescite, C. F. Kirk & Co., New York, N.Y.

† G. E. Lamp No. BH4.

‡ Orthopedic patients at Kernan's Hospital for Crippled Children were examined through the courtesy of Dr. Allen R. Voshel and his staff. Ambulatory patients with healing tuberculosis were examined at the Baltimore City Hospital through the courtesy of Dr. Allen Hartz and staff. The remaining patients were convalescent from various infections at Sydenham Hospital.

one patient whose circulation time does not fall at or below that line, and that was a patient on whom but a single determination was made. The other points that lie to the right of the line are single determinations on patients who had several measurements, the average of which in each case falls at or below the upper limit of normal. It is realized that as more data are accumulated, there may have to be some revision of this arbitrary line.

Results

Table I summarizes the data on the 35 patients with proven diphtheria who were followed by this method with an average of more than five determinations per patient.

TABLE I

Survey of 35 Patients Studied

	Examined	Abnormal C.T.	Abnormal Measurements	Average Maximum Prolongation above U.L.N.* (sec.)	Average Day of Dis. when C.T. last above U.L.N.
Patients with clinical failure. (4 deaths)	7	7	26	10	39†
Patients with ECG *and* ausculatory evidence of myocarditis but no failure.	5	4	17	5	36
Patients with ECG *or* ausculatory evidence of myocarditis but no failure.	9	4	8	2.5	19
Patients with no other evidence of circulatory involvement.	14	4	10	2.5	19
Total Patients	35				

* U.L.N. = Upper limit of normal as defined by the solid line in Figure 1.

† Patients who died are excluded from this figure.

From this table, we can see that a good many of the patients have prolonged circulation times who do not show clinical evidence of circulatory inefficiency. In fact, there were three patients who had circulation times at least double their normal values, without any evidence of cardiac failure as they lay in bed. This would lead one to believe that this test is much more sensitive to changes in the circulatory system than are the palpating hand, the stethoscope or the sphygmomanometer.

Illustrative Cases

Case 1, F.H. #35226, a 70-year-old white female was admitted with a six day history of sore throat, and a three day story of respiratory obstruction that was relieved by tracheotomy at another hospital. On the day before admission cultures were reported to show C. diphtheriae and she was given 60,000 units of diphtheria antitoxin. Physical examination on admission revealed

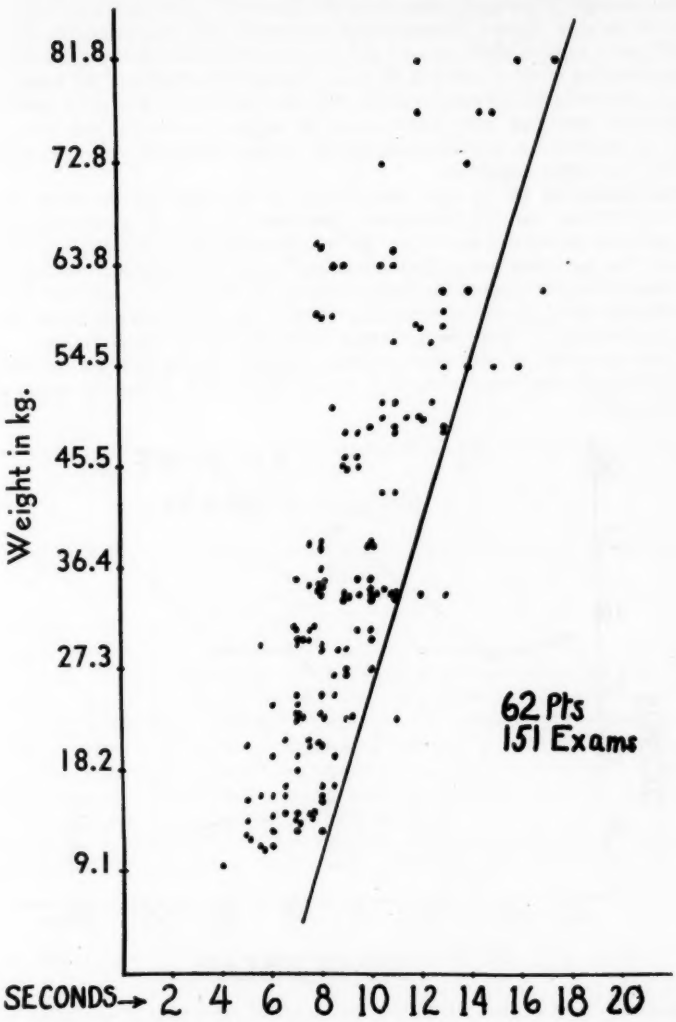


FIG. 1. Variation of the normal circulation time with weight. The line represents the upper limit of normal in 95% of the tests.

an acutely ill elderly woman with a tracheotomy tube in place from which could be suctioned much thick brownish-white material. T. 37.8° C., P. 128, R. 40, B.P. 156/60 mm.Hg., wt. approx. 45.4 kg. The nose was completely occluded with a thick yellowish membrane that could not be removed. The soft palate and pharynx were so swollen that neither the tonsils nor the posterior pharynx could be visualized. The tissues of the upper neck were somewhat boggy but there was no striking adenopathy.

The heart sounds were of good quality. There were showers of fine and coarse rales heard throughout both lung fields, but no change in percussion note. WBC was 18.5 thousand, 88%

polynuclear neutrophils. Repeated cultures from the throat and trachea grew only Esch. coli. Roentgenogram of the chest revealed bilateral central pneumonia. The urine contained albumen +, 10 to 15 WBC, and 1 to 5 granular casts per high power field in a centrifuged specimen. ECG's showed progressive inversion of the T waves in all leads. During the first week in the hospital she made satisfactory progress under intensive penicillin and later streptomycin therapy. A number of large pieces of definite membrane were sucked out of the trachea. On the 15th day of disease it was noted that her heart sounds were poorer in quality, that her respirations were more rapid and that she was becoming slightly edematous.

The next morning she seemed worse. At 8:30 A.M. her circulation time was 21 sec. At 2:30 P.M. she was given 1.2 mg. digitoxin intravenously. Two hours later her circulation time had fallen to 14.5 sec. and after six hours it was 13 sec. She was maintained on at first 0.1 mg. digitoxin daily, then 0.2 mg. but her edema increased and her urinary output decreased until the day before death when it ceased. Daily ECG's showed no digitalis effects. Her blood pressure gradually fell to 100/40 mm.Hg. Terminal blood chemistries revealed an NPN 78 mg./100 cc. blood, sodium 129 mEq./l., chlorides 76.4 mEq/l., and potassium 8.7 mEq/l. At no time was her venous pressure over 15 cm. of water and terminally her veins were completely collapsed. On the 24th day her pulse dropped into the sixties and became irregular. An ECG showed complete A-V dissociation shortly after which respirations ceased.

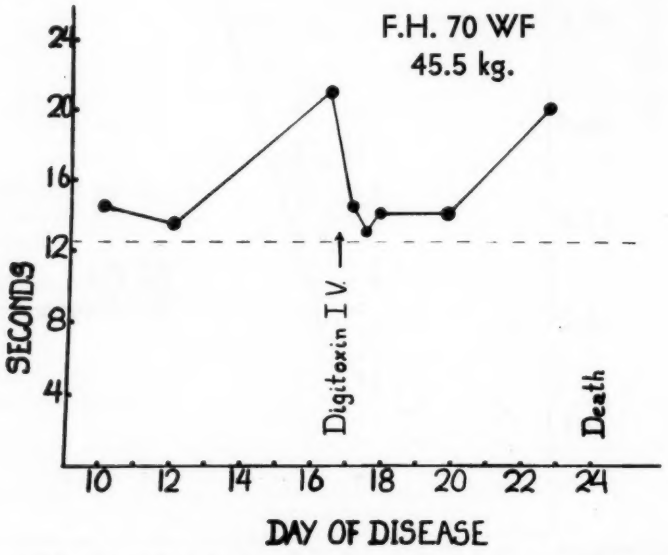


FIG. 2. Circulation times of Case #1. Broken line represents upper limit of normal for her weight.

Case 2, J.W. #34743, a five-year-old white boy was admitted on the fourth day of a severe nasal and faucial diphtheria with bull neck. He was given 80,000 units of diphtheria antitoxin on admission. The next day his apical first sound became mushy, his liver was palpable 1 cm. below the costal margin, and the albumin content of his urine had increased from 1+ to 3+. He was promptly digitalized. By the 11th day of disease his blood pressure had fallen from 100/60 to 76/46 mm. Hg. and he was strikingly pale. By the 14th day he had a gallop rhythm, his systolic blood pressure was still in the seventies, and his liver had increased to 2 cm. below the costal margin. The following day the gallop was more marked and the P waves disappeared from his ECG only to return two days later. The other ECG changes were the development of low voltage and a tendency to left axis deviation. The latter was still present on discharge. By the 19th day his blood pressure was averaging 90/60 mm.Hg., he looked less pale, and his liver edge was at the costal margin. Except for the development of palatal paralysis his course was uneventful from then on. His circulation times are

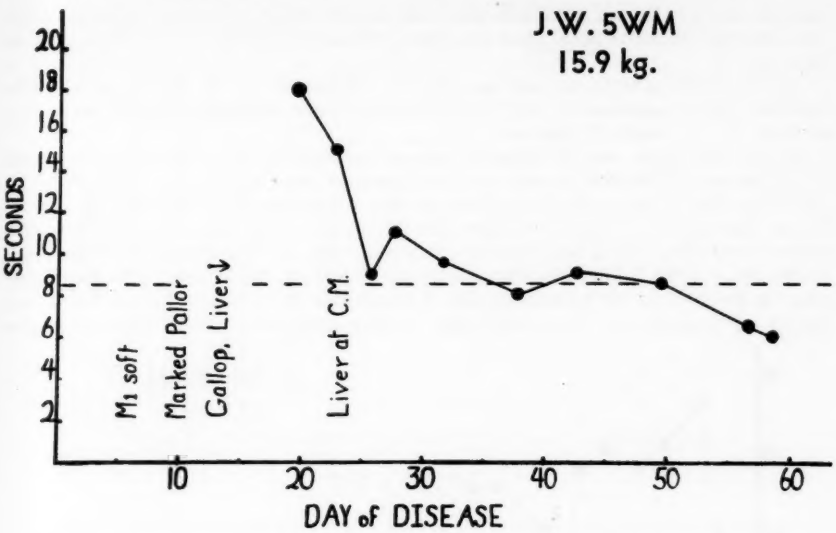


FIG. 3. Circulation times of Case #2. Broken line represents upper limit of normal obtained from Figure 1.

shown in Figure 3.

Case 3, R.R. #34746, an 11-year-old white male was admitted with a three day story of sore throat and cervical swelling. On examination he was found to be a seriously ill boy with tremendous cervical swelling from the jaw to the clavicle. There was a small patch of membrane in the right nostril. The tonsils met in the mid-line and were covered with membrane that extended up over the whole soft palate. Culture of his throat yielded beta hemolytic str., and virulent C. diphtheriae. His urine contained 1+ to 3+ albumen for the first 11 days in the hospital. He was immediately given 100,000 units of diphtheria antitoxin and started on penicillin. The next day there was a decrease in the apical first heart sound, but the ECG was normal.

On the 10th day of disease, a further decrease in the intensity of the first heart sound was noted and the next day the ECG disclosed a complete A-V dissociation with left bundle branch block that

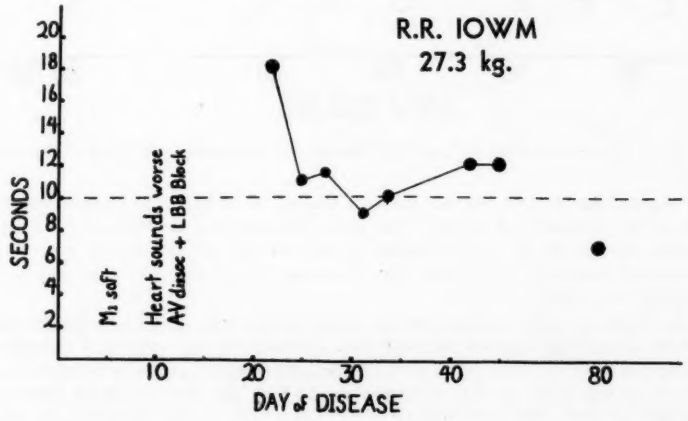


FIG. 4. Circulation times of Case #3. Broken line represents upper limit of normal.

lasted for two days. He was immediately digitalized and never showed any evidence of cardiac failure other than the circulation times which are shown in Figure 4. Digitalis was discontinued on the 30th day.

Case 4, P.O'G. #34771, an eight-year-old white boy admitted on the first day of a tonsillar diphtheria with a temperature of 39.4° C. and moderate cervical adenopathy. Cultures revealed beta hemolytic str. and virulent C. diphtheriae.

He was given 80,000 units of diphtheria antitoxin and penicillin for six days. His course seemed entirely benign until the 28th day when the apical first heart sound was thought to be distinctly soft and mushy. His circulation time rose to abnormal levels and remained there until the 40th day when he was digitalized in 24 hours. Four hours after the last dose his circulation time had dropped to within normal limits only to rise again over the ensuing few days to practically its former height. During this time his P-R interval became prolonged to 0.24 sec. and returned to normal in three days. On the 49th day the maintenance dose of digitalis was increased from 0.75 to 1.0 cat units per day and four days later his circulation time was back within normal limits. This increased dose

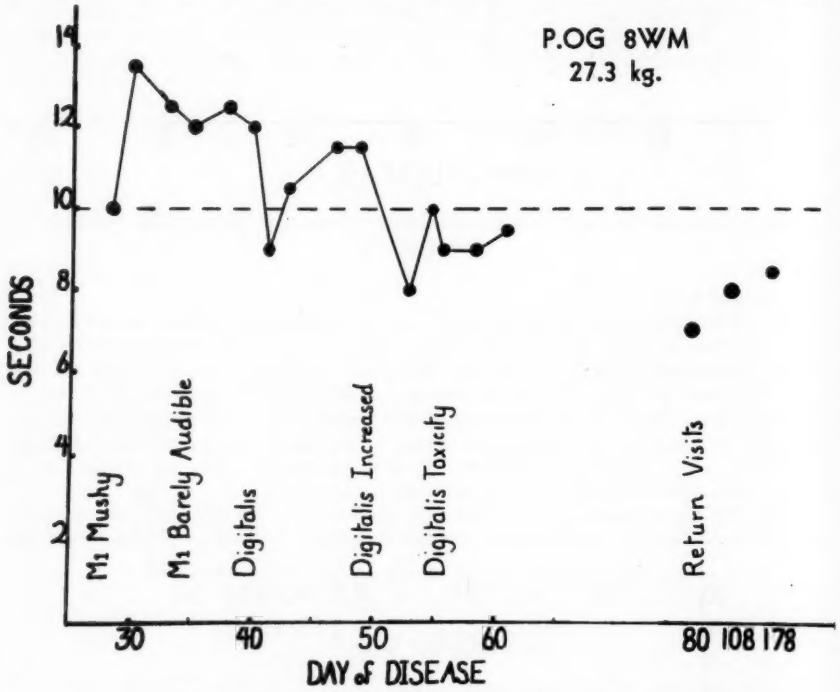


FIG. 5. Circulation times of Case #4. Broken line represents upper limit of normal.

was well tolerated for six days, but then his pulse dropped to 60 and he had some coupled beats but no return of the increased P-R interval. One dose of digitalis was omitted and three days later it was discontinued entirely. He was discharged on the 67th day with persistently poor heart sounds which were still noticeable 6½ months after the onset, though his circulation time and exercise tolerance remained normal.

Case 5, B.D.H. #34954, a three-year-old Negro female was admitted on the seventh day of disease with a membrane limited to the tonsils. Cultures yielded virulent C. diphtheriae. On the 19th day of disease she developed a harsh systolic murmur which gradually decreased in intensity, but was still present when she was discharged on the 35th day. Her circulation times are shown in Figure 6.

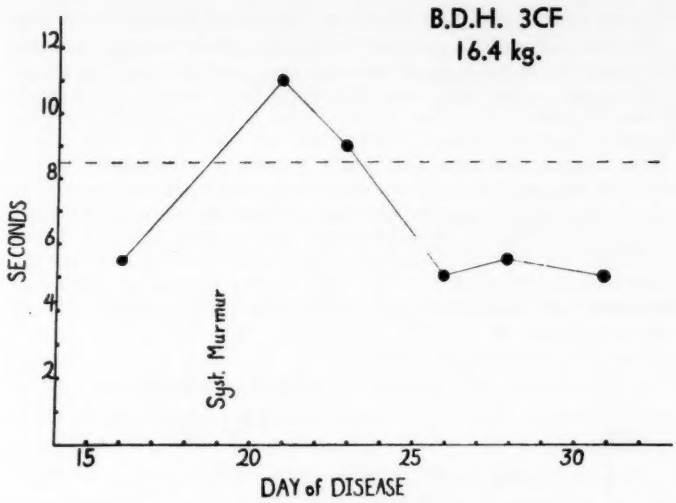


FIG. 6. Circulation times of Case #5. Broken line represents upper limit of normal.

Case 6, W.B. #34808, an eight-year-old white boy was admitted with a 24 hour history of sore throat. Bilateral tonsillar membranes were found, cultures of which yielded virulent C. diphtheriae and beta hemolytic str. He received 80,000 units of diphtheria antitoxin on admission. On the fifth day his urine which had previously been clear contained 1+ albumen and many red cells. This had cleared by the tenth day. On the 14th day he had a rash, thought to be due to the horse serum. Four electrocardiograms were identical and within normal limits. At no time was there any change in the auscultatory findings.

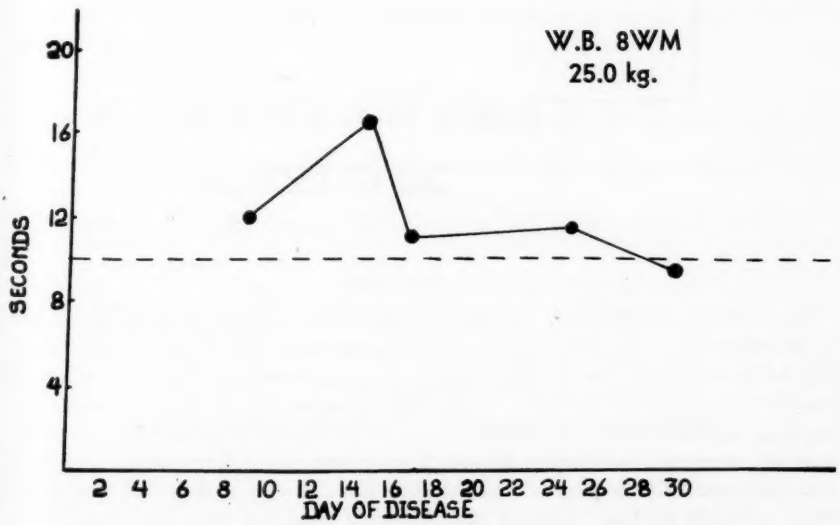


FIG. 7. Circulation times of Case #6. Broken line represents upper limit of normal.

Case 7, W.B. #34955, a 34-year-old white male was admitted with a four day history of sore throat and a two day story of severe sore throat with swelling of the neck. On examination he was found to have greatly swollen boggy tonsils, palate and uvula that were covered with a greyish-white membrane. The anterior cervical nodes were enlarged and there was a thick brawny edema superimposed on them. Cultures of the throat yielded virulent C. diphtheriae. He was given 100,000 units of diphtheria antitoxin intravenously. On the 11th day in the hospital he developed a moderate serum sickness with fever, joint pains and a rash which subsided in five to six days. On the 14th day depression of the first heart sound at the mitral area was noted and on the next day it was practically absent. On the 16th day an ECG showed low voltage, a P-R interval of 0.24 sec., and a prolonged Q-T interval (K had increased from an admission value of 0.36 to 0.45). During the remainder of his hospital stay the heart sounds improved only slightly. The ECG returned to normal limits (P-R = 0.20 and K = 0.37) on the 19th day. Since his circulation time remained always within normal limits he was discharged on bed rest on the 31st hospital day.

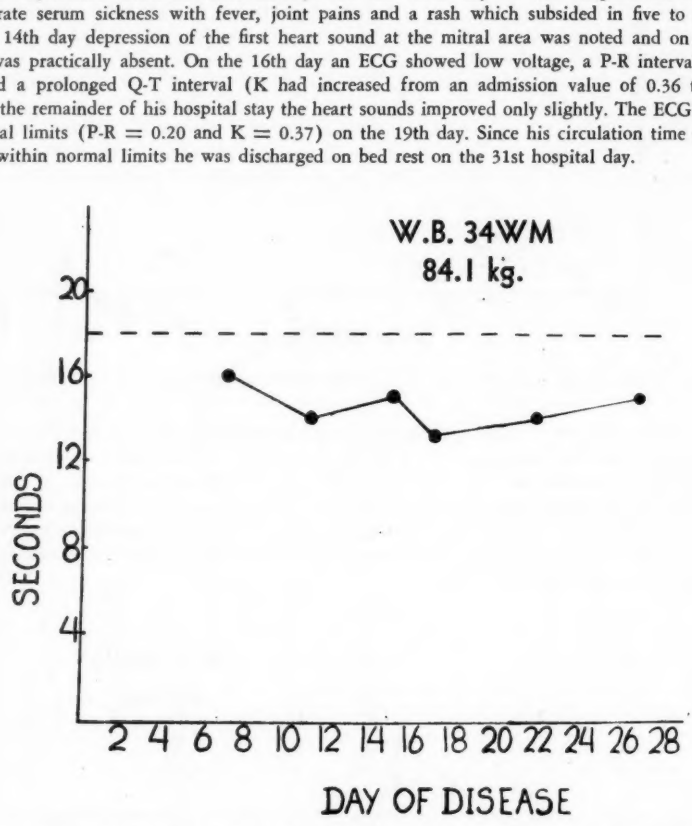


FIG. 8. Circulation times of Case #7. Broken line represents upper limit of normal.

DISCUSSION

There are several ways that this type of measurement can aid the clinician. It may be of considerable prognostic value in severe failure where the return towards normal may be the first indication of improvement. It can help evaluate changes in the heart sounds or the ECG. For example, Case 5 shows a patient who developed a murmur in the third week of disease, the significance of which was in doubt until the circulation time was measured. The contrast between Cases 3 and 7 is striking. Both had distinct ausculatory and ECG findings of a pathologic nature. Neither of them had clinical evidence of failure yet Case 7 showed entirely normal circulation times while Case 3 had a marked prolongation, the full extent of which was never measured.

Prolongation of the circulation time may be the only indication of cardiac embarrassment. Case 6 is a good example of this, but in some of the other cases the circulation time was so equivocal as to be significant only in retrospect when it was found after recovery that the patient's usual circulation time was well below the upper limit of normal where it had hovered during his illness.

The long duration of the circulatory inefficiency is emphasized by Cases 2, 3 and 6. Such measurements can be very helpful in deciding when it is safe for the patient to resume activity. Case 3 was discharged before his circulation time came to normal since he was in the hospital before the normal series was far enough advanced to be any help.

Finally the recurrent problem of digitalis can be studied this way. Cases 1 and 4 suggest that the failure of diphtheritic myocarditis can be ameliorated by adequate digitalis therapy. Case 3 shows that it is possible to recover from heart block in the presence of digitalis. The significance of the fact that his circulation time returned to pathologic levels after digitalis was discontinued on the 30th day is open to question.

Gibson and Evans[3] (1937) showed that the blood volume is markedly increased in chronic congestive failure and it seems logical to assume that this increase contributes to the prolongation of the circulation time. Since there is a decrease in blood volume in diphtheria (Dieckhoff[4] 1943) the prolongation of the circulation time in these cases is all the more significant.

Summary

The circulation time has been studied in 35 cases of diphtheria with repeated measurements. It is a useful guide in judging the severity of myocarditis, and it suggests that digitalis can relieve the failure of diphtheritic myocarditis.

Acknowledgements

We are indebted to Dr. Marcy E. McMillan and Miss Bertha M. Baltus for their assistance with the patients.

References

1. Lange, K., and Boyd, L. J., Use of fluorescein to determine adequacy of circulation, Med. Clin. N. Am. **26**:943, 1942.
2. Witzberger, C. M., and Cohen, H. G., Circulation time in infants and young children determined by fluorescein method, J. Pediat. **22**:726, 1943.
3. Gibson, J. G., and Evans, W. A., Clinical studies in blood volume: changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure, J. Clin. Investigation **16**:851, 1937.
4. Dieckhoff, J., Über störungen des Mineralstoffwechsels und Capillarpermeabilitat bei schweren Infectionskrankheiten bzw. experimenteller Diphtherie- und Dysenterieintoxikation, Klin. Wchnschr. **22**:378, 1943.

Spanish Abstract

Tiempos de Circulacion de la Fluoresceina en la Difteria

Para evaluar mejor la miocarditis difterica se han estudiado los tiempos de circulación de 35 pacientes, por una modificación del método de Lange y Body (1942). En la figura 1 se presentan unas series de control normal, donde los tiempos son trazados en oposición del peso del paciente. Noventa y cinco por ciento de las determinaciones están a la izquierda de la linea gruesa, o sea que hay cerca

de una probabilidad en 20 de que una simple determinación en un paciente normal, de un valor a la derecha de la linea.

En la tabla se presentan los resultados de tal estudio en 35 pacientes, la cual demuestra buena correlación con los hallazgos clínicos en los casos graves, y aún va mas allá apuntando que algunos pacientes sin signos auscultatorios o electrocardiograficos de miocarditis, pueden tener aumentados los tiempos de circulación por una pocas semanas.

Se describen en detalle siete casos de variable gravedad. Las medidas del tiempo de circulación en dos de estos, sugiere que la terapeutica digitalica que recibieron fué definitivamente beneficiosa; otra ilustra el hecho de que los cambios auscultatorios y electrocardiograficos no siempre van asociados con un aumento del tiempo de circulación. Se cree que se trata de un método util para evaluar la gravedad de la miocarditis difterica.

Nashoba Associated Boards of Health

THE INCIDENCE OF BREAST FEEDING IN HOSPITALS IN THE UNITED STATES

By KATHERINE BAIN, M.D.
Washington, D.C.

THE INCIDENCE of breast feeding is of more than academic interest. During the war various agencies, such as the War Production Board and the Office of Price Administration, repeatedly sought such information from the Children's Bureau for use in determining civilian needs for supplies and as a basis for rationing programs. The Army sought such data about each country to be occupied or liberated, in order that stock piling of food for the civilian population for the emergency period could be adequate yet kept to a minimum. Aside from being of value in the solution of emergency problems, knowledge of the incidence of breast feeding in this country is a basic fact about our culture which has validity anthropologically. Any program to change a child-rearing practice needs to rest on a foundation of knowledge of the common existing pattern, as well as on scientific evidence in favor of a different method.

The statement is frequently made that the incidence of breast feeding is declining in the United States.[1,2] Though such a statement, which is based on a collection of individual impressions may well be true, there exist no data to confirm it. Studies of breast feeding in the United States have been few and have been so limited in extent that neither the amount of breast feeding nor the trend in the practice have been known.[3-6]

In some countries information is more readily obtainable, either because they are small countries with homogeneous populations, or because their clinics for health supervision cover a large proportion of the infant population. A report of the Ministry of Health of Great Britain in 1944 estimates that 80% of the babies leave the hospital breast fed, at the end of three months 50%, and at the end of six months 40% are still on the breast.[7] The Plunket Society in New Zealand in 1943, on the basis of data obtained on infants under their supervision (78% of all infants of European stock), estimated the incidence of breast feeding in New Zealand as 89% at two weeks, 71% at three months, and 46% at six months of age.[8] In one sector of Oslo, Norway, in 1944, 88% of the infants born were supervised in the health stations. Of these infants a high percentage were breast fed—96% at two weeks, 88% at three months, and 82% at six months.[9]

COLLECTION OF DATA

When in the summer of 1945 schedules were being formulated for collecting hospital data as part of the American Academy of Pediatrics Study of Child Health Services, the decision was made by the executive staff to include certain questions relating to patterns of hospital practice. Some questions were designed to be used as criteria of quality of care. Others were added to produce factual data on practices, irrespective of opinions as to whether the practices were good or bad. The question relating to breast feeding of newborn infants is in the latter class and forms the basis for this report.

From the American Academy of Pediatrics Study of Child Health Services and the Division of Research in Child Development, Children's Bureau, Federal Security Agency, Washington, D.C.

Read at the Annual Meeting of the American Pediatric Society, May 24, 1948, Quebec, Canada.
(Submitted for publication May 25, 1948.)

Schedule I-D, which contains this question, was designed for hospitals of 25 or more beds. It was intended to be filled in by a pediatrician on a visit to the hospital. Though this technic was followed in many places, in others non-medical field agents obtained the data, or the schedule was used as a mail questionnaire. Since the question is a simple one, not subject to personal interpretation, the variation in method should not affect the results.

The schedule calls for a one-week record of all infants discharged alive from the newborn nursery. Age at discharge is classified as under eight days, or eight days and over. The types of feeding at discharge specified are: breast only, breast and bottle, and bottle

TABLE I

PROPORTION OF HOSPITALS* REPORTING ON TYPE OF INFANT FEEDING

	Total hospitals	Reporting hospitals	
		Number	Percent
Whole country	3,500	2,513	72
Regions:			
Northeast	523	363	69
East and Central	990	663	67
Southeast	744	598	80
Southwest	293	243	83
Mountain and Plains	583	397	68
Pacific	367	249	68
County group:			
Metropolitan-adjacent	2,104	1,465	70
Isolated	1,396	1,048	75
Hospital size:			
25–99 beds	2,212	1,571	71
100–299	929	680	73
250 or more	359	262	73

* Hospitals of 25 or more beds which accept women for delivery.

only. To supply the data, someone, usually the head nurse, went through the past week's discharge records. If data were not readily available, a record was kept for a week and forwarded to the field agent. The collection of the data took place at different times in different states, from the spring of 1946 through the following year.

There are in the continental United States 3,500 hospitals of 25 or more beds which accept women for delivery. Though the hospitals under 25 beds, which are not included in this study, represent 35% of all hospitals giving any maternity care, they contain only 6% of the total beds. The great bulk of the hospital deliveries in this country, therefore, takes place in the 3,500 hospitals considered here. Of these hospitals 2,513 or 72% supplied complete data on the breast-feeding question. There was little variation in the proportion of the returns in different parts of the country. Two-thirds or more of the eligible hospitals in all regions supplied the data. (Table I)

For the purposes of the Academy Study the usual classification of counties into urban

and rural on a straight population basis was not considered adequate. A somewhat more elaborate classification was used involving two factors—population and proximity to a densely populated area. This classification has been described elsewhere in detail.[10] Somewhat oversimplified, the classification is this: the first class, metropolitan-adjacent counties, represents cities of 50,000 or over with the surrounding counties, which taken together form a metropolitan medical service center; the second group, isolated counties, are those which neither have a city as large as 50,000 population, nor are adjacent to a metropolitan center. In these two county groups the percentage of hospitals supplying data on breast-feeding was 70% and 75% respectively. (Table I).

TABLE II

INFANTS ON SPECIFIED FEEDING AT TIME OF DISCHARGE

	Number				Percent		
	Total	Breast only	Breast and bottle	Bottle only	Breast only	Breast and bottle	Bottle only
Whole country	39,171	14,931	10,565	13,675	38	27	35
Regions:							
Northeast	7,054	1,638	1,113	4,303	23	16	61
East and Central	14,682	5,332	4,454	4,896	36	30	34
Southeast	6,439	3,552	1,707	1,180	55	27	18
Southwest	2,505	1,173	890	442	47	35	18
Mountains and Plains	4,586	2,024	1,272	1,290	44	28	28
Pacific	3,905	1,212	1,129	1,564	31	29	40
County group:							
Metropolitan-adjacent	29,616	10,540	7,888	11,188	36	26	38
Isolated	9,555	4,391	2,677	2,487	46	28	26
Hospital size:							
25–99 beds	13,738	5,888	3,610	4,240	43	26	31
100–249	15,419	5,192	4,334	5,893	34	28	38
250 or more	10,014	3,851	2,621	3,542	39	26	35

One other breakdown was employed—by size of hospital. Small hospitals (25 to 99 beds), medium size (100 to 299 beds), and large (250 or more beds) gave almost identical proportions of returns. (Table I)

This sample of 2,513 hospitals, therefore, represents more than two-thirds of all hospitals in the United States of 25 or more beds admitting maternity patients and is representative of hospitals in all regions, in rural and urban areas, as classified in this study, and in hospitals of different sizes. In these hospitals there occurred during the Study year 1,485,000 births, 65% of all those occurring in eligible hospitals.

RESULTS

The data obtained from these hospitals in a one-week sample contained the feeding records at discharge of 39,171 infants.

TABLE III

PERCENT OF INFANTS ON DIFFERENT TYPES OF FEEDING, BY REGIONS AND STATES, RANKED BY PERCENT ON BOTTLE ONLY

Region and state	Breast only	Breast and bottle	Bottle only
Northeast	23	16	61
New Hampshire	27	1	72
Connecticut	20	10	70
Massachusetts	21	12	67
Maine	26	7	67
New York	24	18	58
Vermont	32	16	52
Rhode Island	25	40	35
Pacific	31	29	40
Washington	38	21	41
California	27	33	40
Oregon	42	22	36
Nevada*			
East and Central	36	30	34
Delaware	24	27	49
Maryland	42	11	47
Wisconsin	28	30	42
New Jersey	37	21	42
Illinois	35	30	35
Pennsylvania	40	28	32
Ohio	27	42	31
Michigan	42	28	30
Indiana	39	32	29
Dist. of Columbia	43	28	29
Mountain and Plains	44	28	28
Colorado†			
Kansas	31	29	40
Iowa	42	23	35
South Dakota	49	20	31
Missouri	48	23	29
Montana	48	24	28
North Dakota	42	32	26
Idaho	28	47	25
Nebraska	35	41	24
Minnesota	49	32	19
Wyoming	54	27	19
Utah	56	30	14
Southeast	55	27	18
Virginia	37	36	27
Florida	48	26	26
Georgia	64	13	23
West Virginia	56	24	20
Louisiana	59	22	19
North Carolina	63	20	17
Arkansas	63	21	16
Kentucky	38	46	16
Mississippi	57	29	14
Tennessee	64	24	12
Alabama	60	29	11
South Carolina	60	30	10
Southwest	47	35	18
Texas	43	39	18
New Mexico	36	46	18
Oklahoma	53	29	18
Arizona	70	17	13

* No report.
† Inadequate reporting.

Table II shows the proportion of these infants on the specified types of feeding. Approximately one-third were on artificial feeding only, and two-thirds on breast or mixed feedings. The proportion on bottle only, i.e., presumably completely weaned at time of discharge, is less for isolated counties than for metropolitan and adjacent counties, 26% versus 38%. This finding; namely, a greater incidence of breast feeding in areas away from metropolitan centers, is not unexpected. What is less understandable is the evidence that the incidence of bottle feeding is greater in middle-size hospitals than in small or large ones, a finding that is constant in both county groups.

The most striking fact revealed by this material is the wide regional differences. (Table II) The northeast region (New England and New York) reported 61% of the infants on bottle only at time of discharge, while in the southeast and southwest the proportion was only 18%. All the states in the northeast region, except Rhode Island, reported more than 50% of their infants on bottle only at time of discharge. (Table III) Moreover no states other than these six in the New England region had an incidence of bottle feeding as high as 50%. At the other end of the scale the states which reported more than 50% of their infants entirely breast fed on discharge were all in the southeast or southwest, with the exception of two mountain states. The states with the lowest incidence

TABLE IV

NUMBER AND PERCENT OF INFANTS ON DIFFERENT TYPES OF FEEDING, BY AGE AT DISCHARGE

Age at discharge	Number				Percent		
	Total	Breast only	Breast and bottle	Bottle only	Breast only	Breast and bottle	Bottle only
All ages	39,171	14,931	10,565	13,675	38	27	35
Under 8 days	22,685	9,172	6,449	7,064	41	28	31
8 days and over	16,486	5,759	4,116	6,611	35	25	40

of bottle feeding are South Carolina and Alabama with 10% and 11% respectively. The states with the highest incidence are Connecticut and New Hampshire with 70% and 72%.

The length of stay in hospital appears to have some influence on the type of feeding. Infants discharged under eight days had a higher incidence of breast feeding than those discharged later. (Table IV) In this latter group are of course the infants who are premature and also those that have been ill, but these abnormal infants could hardly account for the difference. One is inclined to believe that infants discharged from hospital early are less apt to have been weaned at the time of discharge. Fifty-eight percent of the infants were discharged before the eighth day.

DISCUSSION

The data presented in this paper represent the first nation-wide survey of the incidence of breast feeding in hospitals in the United States. The material in this paper is limited

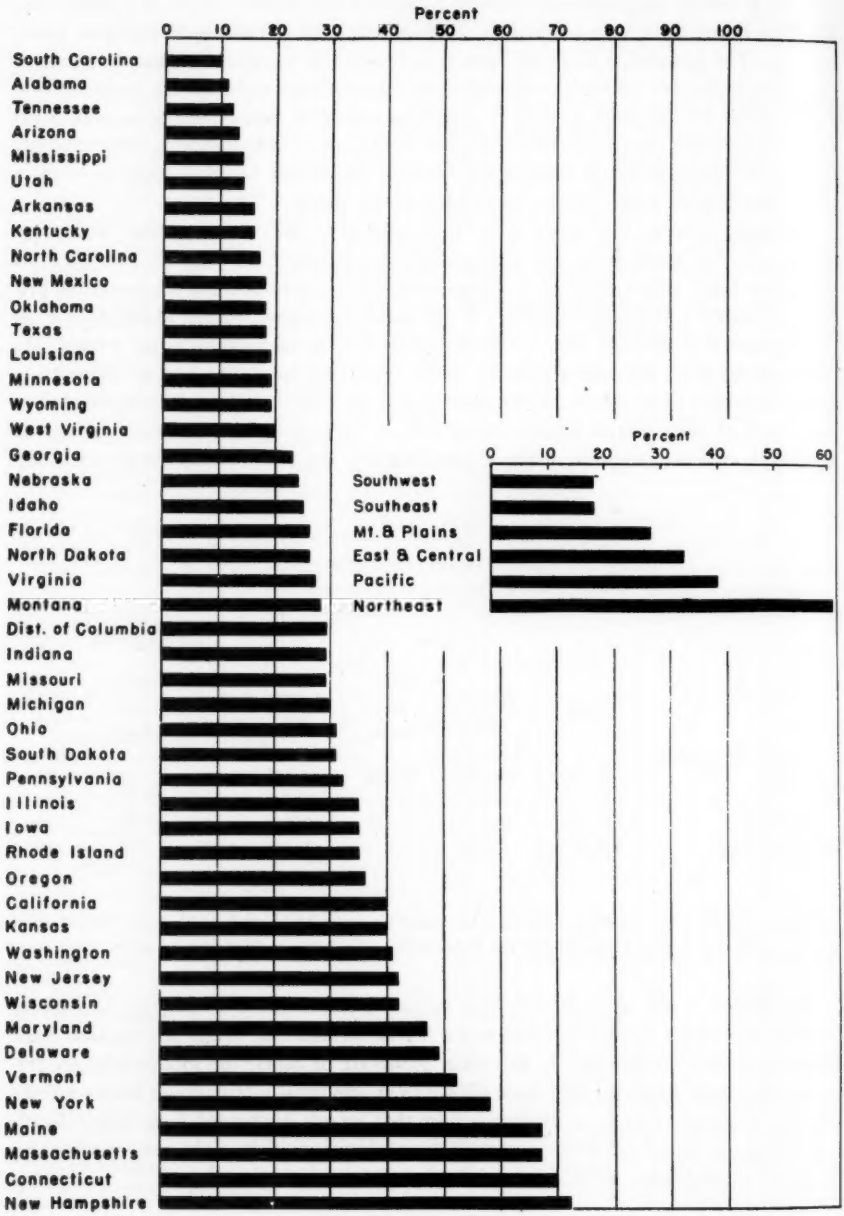


FIG. 1. Percent newborn infants receiving no breast feeding at time of discharge from nursery, by state and region.

to the newborn period, and what happens after that period is a matter of conjecture. Presumably an infant discharged from hospital on bottle only will not be a breast fed baby. Those on breast and on mixed feedings are potentially breast fed infants. How many remain on the breast to the age of three months or six months is unknown.

The question of trend still remains unanswered. Later studies will be needed to show increase or decrease in the incidence of breast feeding.

Conclusions

Data comprising the first nation-wide survey of the incidence of breast feeding in hospitals in the United States are presented.

More than two-thirds of all hospitals of 25 or more beds admitting women for delivery are included in the study. Coverage was equally good for all regions, for urban and rural communities, and for small, medium size, and large hospitals.

For the United States as a whole, one-third of the infants were weaned at the time of discharge from the hospital and two-thirds were on breast or mixed feedings.

A smaller percentage of breast feeding occurred in hospitals in or near metropolitan areas, as contrasted with areas removed from metropolitan centers. A lower percentage of breast feeding occurred in medium-sized hospitals as contrasted with small or large hospitals.

There are striking regional differences, in the northeast the percent of infants on bottle feeding only—at time of discharge—being 61%, as contrasted with an incidence of 18%, in the southwest and southeast.

Among infants discharged from hospital under eight days of age the incidence of breast feeding was higher than among those who remained longer.

References

1. MacNeill, N. M., Can we retrieve breast-feeding? Pennsylvania M. J. **51**:137, 1947.
2. Garland, J., and Rich, Mabel B., Duration of breast feeding; comparative study, New England J. of Med. **203**:1279, 1930.
3. Grulee, C. G., Breast Feeding, Proc. Interst. Postgrad. M. A. North American (1943), 1944, p. 135.
4. Byington, G. M., Incidence of breast feeding in Detroit, Psychosom. Med. **7**:173, 1945.
5. Wegman, M. E., Marchante, R. F., and Kramer, M., Infant mortality and infant feeding in Puerto Rico; preliminary note, Puerto Rico J. Pub. Health and Trop. Med. **17**:228, 1942.
6. Sedgwick, J. P., Preliminary report of study of breast feeding in Minneapolis, Am. J. Dis. Child. **21**:455, 1921.
7. Waller, H., Early failure of breast feeding, Arch. Dis. Childhood **21**:1, 1946.
8. The Royal New Zealand Society for the Health of Women and Children (Plunket Society), Annual Report, 1942-43.
9. Toverud, K. Utheim, Beretning om de forste 6 ars arbeid ved Oslo kommunes Helsestasjon for mor og barn pa Sagene (1939-1944), Fabritius and Sonner, Oslo, 1945.
10. Hubbard, J. P., Penell, Maryland Y., and Britten, R. H., Health services for rural child; availability of hospitals, physicians and dentists in service areas, J.A.M.A., **137**:337, 1948.

Spanish Abstract

La Proporcion de Alimentacion por el Pecho en los Hospitales de los Estados Unidos

Los datos presentados, obtenidos en la American Academy of Pediatric's Study of Child Health Services, son las primeras cifras nacionales sobre la proporción de alimentación por el pecho en los hospitales de los Estados Unidos.

Se obtuvo un record de una semana de la alimentación de todos los niños (por debajo de ocho dias, de ocho dias y mayores) al tiempo de la salida de las secciones de recién nacidos del 72% de los 3,500 hospitales de 25 o mas camas que admitian mujeres para dar a luz. Este ejemplo fué de casos típicos de hospitales en general tanto rurales como urbanos, tomado en hospitales de pequeña o larga capacidad.

La forma de alimentación al tiempo de darseles de alta en un resumen de 39,171 niños, fué como sigue: A una tercera parte de estos casos se les daba solamente biberón cuando dejaron el hospital, las dos terceras partes restantes eran amamantados por la madre o a pecho y biberón en conjunto.

La proporción de niños enteramente destetados al ser dados de alta del hospital era menos en areas distantes de centros metropolitanos, y menos tambien en pequeños o grandes hospitales, en comparación a los de un termino medio de 100 a 249 camas.

Existen divergencias regionales con referencia a la alimentación de pecho. En la región nordeste 61% de los niños salieron del hospital con alimentación artificial, comparado con el 18% en el sur y suroeste. Los estados en que la proporción de niños con alimentación artificial completa excedía al 50%, fueron en el area nordeste. Los estados con la mas alta proporción fueron Connecticut y New Hampshire con 70 y 72%. Los estados con mas baja proporción de alimentación con botella fueron South Carolina y Alabama con 10 y 11% respectivamente.

El grupo de niños salidos menores de ocho dias tuvo un mas alto porcentaje de alimentación por el pecho que los que tenian ocho dias o mas.

Children's Bureau, Federal Security Agency

Pediatrics

VOLUME 2 SEPTEMBER 1948 NUMBER 3

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Special Report

FROM THE COMMITTEE ON SCHOOL HEALTH AND THE COMMITTEE ON RHEUMATIC FEVER

RHEUMATIC FEVER AND THE SCHOOL CHILD

A Statement to Guide School Health Authorities

This joint report of the Committees on School Health and Rheumatic Fever of the American Academy of Pediatrics has been prepared as a guide to school authorities in determining what can be done about this disease through the schools.

The school occupies a unique position in relation to rheumatic fever control. Rheumatic fever causes more deaths than any other disease in children of school age. A first attack usually occurs in children at the age when they are in the first or second grade and recurrences are most common up to the age when children are leaving high school. The insidious onset of so many cases during the school years suggests that teachers and others in daily contact with school children should be aware of early signs and symptoms which may mean acute rheumatic fever.

The periodic school health examination when done hastily without removal of clothing may miss children with rheumatic heart disease. On the other hand, children may be labeled with the diagnosis of a rheumatic heart because a heart murmur was wrongly interpreted. This serves to emphasize the opportunities as well as the difficulties of discovering rheumatic fever and rheumatic heart disease in school children.

IMPROVEMENT OF SCHOOL MEDICAL PROCEDURES

The American Academy of Pediatrics believes the problem of what to do about rheumatic fever through the schools is an integral part of what should be done about the health of all school children. The following recommendations, while pointed towards case-finding and health supervision of the rheumatic child, will, if applied, lead to better health service for all school children.

The periodic school medical examination should be improved:

1. By obtaining a health history of the child from the parent and the teacher, if possible, at the time of the child's examination.
2. By being performed without haste and with the child disrobed.
3. By the employment of physicians trained in pediatrics, if possible. Where this is not feasible, arrangements should be made for giving physicians who make school medical examinations additional clinical training in normal child growth and development as well as in children's medical problems including rheumatic fever and heart disease.
4. By allowing time for the physicians to plan with the nurse and parent for medical attention. The examination is then more likely to be of greater aid in getting medical care for school children who need it.

The follow-up activities of the nurse should be to see that the children in need of medical attention are referred to physicians and that every effort is made to have needed care given. Special health and welfare resources in the community should, if necessary, be brought to the attention of the family and the child's physician.

Daily Observation of Children with Special Reference to Rheumatic Fever

Nurses and teachers should be more alert to substandard health in all school children. School absence due to illness or vague disorders, if investigated, may disclose early cases of acute rheumatic fever. In order to make use of the school's daily contact with the child, there should be daily observation of pupils for signs and symptoms suggestive of substandard health. Among these signs and conditions which should bring children to the attention of the teacher or parent are:

1. Failure to gain weight
2. Pallor
3. Poor appetite
4. Fatigue
5. Frequent colds and sore throats
6. Tonsil and adenoid operations (because it may indicate previous sore throats)
7. Scarlet fever or any known streptococcal infection
8. Unexplained nosebleeds
9. Unexplained fever
10. Pains in arms, legs, and joints
11. Unusual restlessness, irritability, twitching or jerky motions
12. History of previous rheumatic fever
13. Behavior and personality changes
14. Decreasing accomplishments in school by a child who has previously done well.

Children reported by the teacher as showing evidence of substandard health should be medically reviewed by the school nurse or physician to select children who need further medical investigation. A personal interview by the school physician or nurse with parents either in school or through a home visit is recommended to emphasize the need for further medical attention for the child through the physician of the family's choice.

Schools have tended to place too much emphasis on the finding of a heart murmur in the child. This has resulted many times in needlessly restricting the child's physical activities.

Relatively few rheumatic children attending regular school in the intervals between attacks need to have their physical activity restricted. In a group of 1,000* rheumatic children seen ten years after they first came under observation, 783 were alive and of these, more than 80% were able to lead normal active lives except in competitive sports. More than half were able to engage in competitive sports.

Preparation of Teachers in Health Guidance

Teachers should know more about children's health problems, including rheumatic fever. Not only should they be able to recognize children with signs and symptoms of substandard health, but also they should realize the importance of protecting children, especially the rheumatic child, from respiratory infections. Children with early signs of upper respiratory infections should be encouraged to stay home. Health education is especially important for the rheumatic child because the chronic nature of the disease requires, as in tuberculosis, that the susceptible individual learn the special importance of good hygiene. Preparation in health guidance should be given both to teachers in training and to teachers in service. The American Academy of Pediatrics will be glad to cooperate by helping school authorities to locate pediatricians to assist in programs of teacher-training in health.

Rheumatic Fever Diagnostic Service

Because of the difficulty of diagnosing rheumatic fever and rheumatic heart disease, and especially the important point of determining whether or not the process is active, special diagnostic facilities should be available to all physicians, including school physicians, who may advise parents concern-

* Jones, T. D. and Bland, E. F., Rheumatic fever and heart disease; completed ten-year observations on 1,000 patients, Tr. A. Am. Physicians **57**:265, 1942.

ing care of children with possible, potential, or definite rheumatic heart disease. Diagnostic facilities should have the approval of local medical societies. The consulting specialist in rheumatic fever should have electrocardiographic, fluoroscopic, and other necessary laboratory facilities. Every effort should be made to bring this diagnostic service to the attention of physicians who take care of school children. A complete report of the specialist's examination should be sent to all physicians concerned with the care of the child.

The purpose of this service is not only to diagnose rheumatic fever and rheumatic heart disease and to make recommendations as to the health and educational services needed by the child, but also to screen out those children who have heart murmurs but who do not have organic heart disease. It is also useful in regard to placement and removal of children in special schools and classes for the handicapped.

Cooperation with Community Health and Welfare Agencies

Adequate health services for school children calls for close working relationships between medical, public health, social welfare, and educational authorities. The school can improve its services to children by utilizing, at every opportunity, community resources—for example, the use of the clinical teachers of a local medical school to give courses to school physicians, the use of laboratory and clinic services of community hospitals for diagnostic and consultation service, the provision of home or hospital eduation for children who are bedridden, communication with welfare authorities concerning inadequacies in the home environment. These services should be made available to all, but without waste of professional services and of public funds. Close cooperation between the physician, family, school, and other community health and welfare resources is essential.

Recommendations

The school gives an unusual opportunity to attack rheumatic fever. Certain improvements in school health services are needed to make the best use of this opportunity. These recommendations of the Academy will not only be a better approach to rheumatic fever but to other health problems of children. The alertness of teachers and school nurses can bring to medical attention children with signs and symptoms suggestive of rheumatic fever whose condition might otherwise be overlooked. It is also an opportunity through periodic medical examinations to discover unrecognized damage to the heart and to keep under medical supervision known cases of the disease and to make family studies of rheumatic children. It is an opportunity to teach the principles of healthful living to children who have the disease or who are susceptible.

To aid school health authorities to develop a more rational approach in the control of disease, the Committees on School Health and Rheumatic Fever of the American Academy of Pediatrics recommend: (1) that the school medical examination be improved to aid in more accurate recognition and supervision of rheumatic children, (2) that more emphasis be placed on referral by teachers and nurses of pupils believed to be below-par for medical review, (3) that less emphasis be placed on restricting the physical activity of rheumatic children and more attention given to daily observation of pupils for signs or conditions suggestive of rheumatic disease, (4) that there be available, to school health services and the practitioners, diagnostic and consultation services to establish diagnosis, (5) that these services be developed in cooperation with, and by utilization of, existing medical and public health resources in the community.

American Academy of Pediatrics

Committee on School Health

Helen B. Pryor
Thomas E. Shaffer
A. Clement Silverman
Arthur E. Wade
Estella F. Warner
Ernest H. Watson
Harold H. Mitchell, Chairman

Committee on Rheumatic Fever

Harry L. Bacal
Crawford Bost
Stanley Gibson
Arild E. Hansen
John Hubbard
Alexander T. Martin
Hugh McCulloch
George M. Wheatley, Chairman

Communication from

THE COMMITTEE ON FETUS AND NEWBORN

State committees on fetus and newborn have been appointed in 47 states, in four Canadian Provinces and in Hawaii. All of these committees are now confronted with the problem of organizing an active program.

All state programs must have the active cooperation of the state and county medical associations. Following are excerpts from a letter from Dr. Milo Brooks showing how the Southern California Committee has informed their County Medical Association of the program and made a strong bid for its support and cooperation:

". . . The two groups (the Academy and an independent Los Angeles group, previously organized) have now blended into one organization, and with the cooperation of the Bureau of Maternal and Child Health of the State of California Department of Health, the Obstetrical and Pediatric Sections of the Los Angeles County Medical Association and the American Academy of Pediatrics have prepared a tentative program composed of the best features of premature programs now functioning in other cities and states.

"We . . . need (your) cooperation and support . . . and, therefore, humbly make the following requests for:

(1) Approval of the . . . committee as now constituted, or a committee as selected by the Los Angeles County Medical Association, as an advisory committee to work with the city and county Health Departments in the organization and operation of a premature program for Los Angeles County.

(2) Appointment (if the present committee is acceptable) of a representative, preferably a member of the section on General Practice, to the committee.

(3) Presentation of the following recommendations to the Los Angeles City Health Department Commission, and the Los Angeles County Health Department:
   a. To recognize the need for better facilities for the care of premature infants born in Los Angeles County.
   b. To approve and list centers for premature care and/or assist hospitals to establish or enlarge and equip a premature center.
   c. To establish post-graduate nurses' training in the care of premature infants.
   d. To permit the Los Angeles County General Hospital to accept any premature infants born outside the hospital within the limits of their capacity.
   e. To supply the physical necessities for transporting prematures to adequate facilities when aid is requested by the physician in attendance, i.e. nurses, ambulances, oxygen, incubators, etc.
   f. To supply funds for a secretary, or other personnel, which is needed for the proper functioning of the program.
   g. To make prematurity a reportable condition when adequate facilities become available to care for all premature infants born at home or in hospitals where facilities are inadequate.
   h. Investigate premature infants' deaths.

(4) Recommendation to Los Angeles County Supervisor, Raymond Darby, and LeRoy Bruce, Director of the Los Angeles County General Hospital:
   a. To establish a premature care station at the Los Angeles County General Hospital.
   b. To establish at the Los Angeles County General Hospital a post graduate nurses' training center in the care of premature infants.
   c. To permit the Los Angeles County General Hospital to admit any premature infants born outside the hospital within the limits of their capacity."

The letter was signed by members of the committee and carbons were sent to interested individuals. It is hoped that other state committees may benefit by reviewing this procedure.

STEWART H. CLIFFORD, M.D., *Chairman*

Symposium

ON CONGENITAL HEART DISEASES

STANLEY GIBSON, M.D., *Chairman, Chicago, Ill.*

Chairman Gibson, INTRODUCTION:

The fact that we are holding this symposium offers eloquent testimony to the new interest in congenital cardiovascular abnormalities. So long as we had no effective therapy it seemed scarcely worth while for the clinician to concern himself with the niceties of differential diagnosis of the various types of congenital heart disease. The brilliant advances in cardiovascular surgery during the past few years have laid upon the pediatrician the burden of accurate anatomical diagnosis.

In 1939, Gross and Hubbard reported the first successful ligation of a patent ductus arteriosus. In May 1945, Blalock and Taussig described their operation for the relief of congenital pulmonary stenosis. In October 1945, Crafoord and Nylin published the first report of a successful operation for the relief of coarctation of the aorta, and in November 1945, Gross reported the surgical relief of tracheal obstruction due to a vascular ring.

We wish to discuss some of the diagnostic features of these congenital cardiovascular defects, together with the surgical methods employed in their correction.

Dr. John C. Jones, Los Angeles, Calif., THE DIAGNOSIS AND SURGICAL MANAGEMENT OF PATIENT DUCTUS ARTERIOSUS:*

Since Gross in 1938 first successfully ligated a patent ductus arteriosus, physicians have shown greater interest in the accurate diagnosis of congenital cardiovascular lesions and surgeons have been stimulated by a challenge either to alleviate or to cure these malformations. Advances have been made in vascular surgery in the production of fistulous shunts in patients having a tetralogy of Fallot and in the resection of coarctations with end to end anastomosis of the aorta. Experimental surgery has even given promise of successful closure of interauricular septal defects although at this writing I know of none having been attempted in human beings. These newer and more recent spectacular operations have overshadowed the surgical ligation and division of the patent ductus arteriosus which have now become common procedures that no longer create the comment or the attraction they invited so recently as three years ago.

SYMPTOMS AND PHYSICAL FINDINGS

There may be no symptoms whatsoever and the patient may appear well and normal. Palpitation, weakness, ease of fatigue and inability to keep up with the activities of normal children are not uncommon. Tachycardia, fainting attacks, dyspnea on exertion and epistaxis are occasionally complained of and finally, the usual symptoms of cardiac failure and of subacute bacterial endocarditis may be seen in the more acutely ill patient with complications.

Although most of the patients are slim and underdeveloped, some appear normally developed in all respects. Retarded physical growth and development is attributed by Eppinger and Burwell to the shunt of blood from the aorta to the pulmonary artery with a diminution of the peripheral flow. These paitents have no clubbing of the digits nor cyanosis unless there exists another congenital lesion for which the patent ductus arteriosus may be an accommodating fistula or unless the patient is in heart failure.

An active precordial heave and visible pulsation of the cervical vessels may or may not be seen but a palpable thrill is felt over the pulmonic area in the vast majority of patients. The thrill may be systolic or continuous with systolic accentuation and may not appear until the third or fourth year of life. In some of our cases its detection by the mother led to the patient's being examined and diagnosed for the first time. If the thrill is absent in a patient over four years of age one might speculate that the ductus is small.

From the Annual Meeting of the Academy, Dallas, Tex., December 11, 1947.

* From the Thoracic Surgery Department of the Children's Hospital, Los Angeles, California, and the Medical School of the University of Southern California.

The murmur may be absent or easily missed in infants because of the rapidity of the heart rate and the small size of the chest but usually after the third year the murmur is definitely a characteristic one; it is a continuous rumbling "machinery murmur," usually accentuated during systole or early diastole, maximum in intensity in the pulmonic region, and transmitted over the precordium to the back and to the axilla. In all cases in which a continuous murmur was questioned clinically an electric recording of the murmur proved it to be continuous. The second pulmonic sound was increased or reduplicated in almost all our cases.

The vast majority of our patients had an elevated pulse pressure with a low diastolic blood pressure and the latter usually was difficult to measure accurately, there being no sharp point which could be read with certainty. Exercise, exertion and excitement caused a marked increase in the pulse pressure and lowering of the diastolic pressure in most of our cases. Corrigan pulse and pistol-shot sounds over the femoral arteries may be observed in cases with a large ductus. Needless to say, blood pressure readings are taken in both upper and lower extremities to detect coarctation of the aorta.

The heart itself may not be enlarged but usually it is slightly enlarged. Ordinarily the heart rate is increased and the intensity and vigor of the heart action is greater than in the normal; exercise definitely increases the rate and the intensity of the heart beat more than would be expected in a normal patient.

Laboratory Findings

Electrocardiographic studies usually show no abnormality and no axis deviation because the left ventricle pumps a larger volume per minute and the right ventricle must pump against an elevated pressure in the pulmonary arteries, the additional loads more or less counterbalancing one another. Axis deviation should arouse suspicion of the presence of another lesion and a right axis deviation would particularly suggest pulmonary stenosis.

Fluoroscopic and roentgen studies usually demonstrate some cardiac enlargement, prominence of the pulmonary artery, increased pulsation of the heart and great vessels and pulmonary congestion but these are not in themselves specifically diagnostic findings of patent ductus arteriosus but merely confirmatory evidence.

Indications for Operation

In formulating an opinion as to the advisability of surgery in the uncomplicated patent ductus arteriosus one must consider the chances of development of complications in the untreated as against the dangers of surgery. Our experiences in one hundred cases treated surgically justify our advising surgery in all patients with this lesion except those in their thirties or older who have no progressive cardiac hypertrophy or incapacitation by virtue of having had a shunt for so long. We believe the optimum age to be about three years although we have operated on some younger than three. The older the individual in our experience, the more difficult is the operation technically. The vessels of the young individual are far more elastic and their tissues dissect with ease in contradistinction to those of the adolescents and adults. Patent ductus arteriosus complicated by subacute bacterial endocarditis should be operated on after a prolonged and intensive treatment with penicillin. We do not believe that the fact that penicillin may cure bacterial endocarditis justifies advising a patient not to accept surgery. One must assume that the damage done by infection is not eradicated by penicillin, nor does an apparent cure by penicillin necessarily prevent a recurrence of the subacute bacterial endocarditis. The fact remains that the presence of a shunt throws a burden on the heart so that the majority of these patients develop a cardiac hypertrophy; furthermore, the newer technic of dividing the ductus and suturing the wall of the pulmonary artery and aorta not only prevents the chances of re-establishing the shunt but it also offers greater assurance against the development of a subacute bacterial endocarditis. In young individuals there is no sure method of predicting which one will develop cardiac hypertrophy or subacute bacterial endocarditis; and, as long as the surgical morbidity and mortality rate is very low, we believe that it is most urgent to treat these patients surgically.

Operative Technic

Briefly, we employ a postero-lateral transpleural approach, resecting a long segment of the fourth rib posteriorly and with rib spreaders applied we believe this operative exposure far superior to the anterior approach which we used in the first 41 cases. The lung is allowed to collapse and the mediastinal pleura over the ductus is incised and the ductus is dissected all the way around. Cotton

tapes are passed around the ductus to aid in a thorough and complete dissection of the fibrous and areolar tissues about the vessel and the reflection of tissue from the pericardium over the ductus, pulmonary artery and aorta. Four hemostats are placed across the ductus which is then divided between the inner two hemostats as proposed and described by Gross. Then the inner two hemostats are removed and both cuffs of the ductus distal to the remaining hemostats are sutured with fine silk on atraumatic needles. The remaining two hemostats are then removed and the suture line covered with pledgets of fibrinfoam or gelfoam. The mediastinal pleura is then sutured and after the lung is expanded the chest wall is closed in layers without drainage.

Ether-oxygen endotracheal anesthesia has been used in the vast majority of these operations and we prefer it to cyclopropane.

The postoperative care of these patients has been rather simple. Very few have required glucose infusions; blood transfusion is contraindicated except where a hemorrhage indicates its use; and in the last 30 operations only four have required pleural aspirations. Penicillin is now administered for 24 hours before operation and for 72 hours after operation. Usually the patients are discharged from the hospital seven days after operation.

We believe the division of the ductus rather than ligation in continuity should be done in every instance where it is surgically feasible. There is the occasional short ductus which may not appear long enough but if the dissection is thorough the vast majority of them can be "lengthened" and the clamps may encroach a trifle on the walls of the vessels to enable the division of the ductus to be carried out. Mobilizing the aorta and pulmonary artery is a great aid in preparing the ductus for division and the experienced surgeon will have no difficulty getting enough length of ductus to divide it. The division of the ductus insures against re-establishment of the fistula and possible subsequent development of subacute bacterial endocarditis and is therefore preferable to the procedure of simple ligation.

Operative Complications

Recently a detailed account of the postoperative complications in the first 61 patients of this series was reported by the author. In the last 39 cases, only five patients have needed pleural aspirations and only one has had a disturbing complication; namely, a transient pericardial effusion which absorbed spontaneously and which kept the patient in the hospital only 16 days instead of the usual seven days postoperatively. His convalescence was uneventful. Briefly, the complications in 100 successive operations (58 ligations and 42 divisions) are as follows: 27 required pleural aspirations; two developed an empyema necessitating rib resection, both made a good recovery; two of the earlier cases ligated with umbilical tapes, developed aortobronchial fistula at the site of the tied knots, one of which required surgical intervention, the other healed spontaneously and both have been well for a long time. Five patients had a pulmonary atelectasis which cleared with more intensive administration of carbon dioxide and postural treatments. Two patients developed a persistent recurrent laryngeal nerve palsy in spite of meticulous care to avoid injury at the time of surgery. These were earlier cases occurring after ligation and we assume the irritation or pressure of the knots of tape in the close proximity to the recurrent laryngeal nerve caused this complication. There were no wound infections but the incidence of keloid in the supramammary scars was one of the reasons for abandoning the anterior approach.

There were two deaths in the entire series of 100 patients. The first was a child operated on in 1939 who developed Staph. aureus endarteritis about 30 days after ligation of the ductus and died 48 days postoperatively. The ligatures had cut through the walls and a superimposed blood stream infection resulted in vegetations on both pulmonary artery and aortic walls. The other death was an operative mortality from cardiac arrest following hemorrhage during the dissection of the ductus. In the last 40 cases (35 divisions and five ligations) no serious complication has occurred.

Results

The beneficial effects of the operation in children with developmental retardations has been very obvious. Gain in weight, appetite and strength and capacity for activity has been a universal effect. Patients who had palpitation, tachycardia, fainting spells and ease of fatigue were soon completely asymptomatic. A rise in the diastolic blood pressure and a decrease of the pulse pressure was noted either at once or within the first few days after operation. Invariably a decrease in the size of the heart in all those patients who had cardiac hypertrophy before surgery was noted within a month or two afterward.

In all 100 cases a patent ductus arteriosus was found at operation and either ligated or divided; there were no mistaken diagnoses. There are 98 of the 100 cases operated on alive and only one of these is not entirely well, she being a diabetic with a re-established fistula following ligation several years ago and a low cardiac reserve. The 42 patients whose ductus was divided had no consequential residual murmur but ten of the 58 ligations had a continuous murmur which persisted or returned later after discharge from the hospital. The importance of the surgical division of the ductus, rather than ligation, is borne out in this series.

Summary and Conclusions

Since it would appear that the diagnosis of patent ductus arteriosus can be made accurately in such a high percentage of cases and that the surgical treatment of this lesion is highly successful with a low mortality and morbidity rate, we believe surgery is advisable in all cases with this lesion excepting the 35-year-old or older group who have no progressive cardiac hypertrophy and no incapacitation by virtue of their fistula. The optimum age for operation is three years. The vast majority of the patients have a ductus that can be divided and the advantages of division over ligation have been pointed out. Patent ductus arteriosus complicated by subacute bacterial endocarditis should have surgery following intensive penicillin therapy.

Chairman Gibson, Congenital Pulmonary Stenosis:*

Congenital pulmonary stenosis is one of the most frequent anomalies encountered in patients who suffer from congenital heart disease accompanied by cyanosis. Yet congenital pulmonary stenosis rarely exists as a single lesion. It is usually accompanied by a defect of the ventricular septum, overriding of the aorta, and hypertrophy of the right ventricle. This syndrome is known as the tetralogy of Fallot. When one considers the pathology present in this syndrome, it is easy to understand why the patient is cyanotic. In the first place, the stenosis of the pulmonary artery prevents an adequate supply of blood to the lungs for aeration. In the second place, since the aorta overrides the defect in the ventricular septum, some venous blood from the right ventricle flows directly into the aorta. Thus we have both the presence of a venous arterial shunt, and an inadequate supply of blood to the lungs as contributing factors in the production of cyanosis. Dr. Blalock and Dr. Taussig reasoned that if a greater amount of blood could be directed to the lungs, the state of the circulation could be improved, and cyanosis partially or completely removed. This they undertook to accomplish by anastomosing a branch of the aorta, usually the subclavian artery, to the right or left pulmonary artery. Their brilliant success in this bold operation is well known to all of you.

I should like now to outline briefly the symptoms and signs in the typical case of the tetralogy of Fallot. The patient may show cyanosis even in the neonatal period, or it may be several months before cyanosis is noted. At first he may be blue only on crying or other exertion, but after a time the cyanosis becomes constant. Feeding disturbances are frequent and gain in weight is usually slow. Sitting and walking are delayed. Fretfulness and irritability are the rule. In the course of time clubbing of the fingers and toes is seen, and the eyes are suffused.

Physical examination of the heart usually reveals it to be of normal size or only slightly enlarged. On listening to the heart, one hears a more or less harsh systolic murmur, maximal along the left sternal margin at about the second or third interspace. A thrill is palpable in a fair percentage of cases.

The red blood cell count is elevated, sometimes to 10 million or more, and the hemoglobin is correspondingly high.

Roentgenographic and fluoroscopic study is essential for diagnosis. In the A-P view of the chest, one sees a heart that is little if at all enlarged. It is boot-shaped. The apex is blunt and rounded, and the heart appears to lie more or less transversely on the diaphragm. There is a concavity in the region of the pulmonary conus. The lung fields show less than the normal vascularity. When the patient is studied under the fluoroscope, the left anterior oblique view reveals an abnormally clear pulmonary window beneath the arch of the aorta. The concavity in the region of the pulmonary conus, the decreased vascularity of the lung fields, and the clear pulmonary window, all furnish evidence that the pulmonary artery is carrying less than its normal amount of blood.

* From Children's Memorial Hospital, Chicago, Ill.

Hypertrophy of the right ventricle has been mentioned as one of the features of the tetralogy of Fallot. We would therefore expect that the electrocardiogram would show axis deviation to the right, and such is the case. The QRS is usually almost completely downward in Lead I, and upright in Lead III.

Such is a brief sketch of the important findings in the typical case of the tetralogy. One further item of information is essential before operation is undertaken. In about 20% of cases of the tetralogy of Fallot, the aortic arch is on the right. It is important for the surgeon to know the position of the arch before the chest is entered. In the Blalock procedure, the chest is usually entered on the side opposite the arch. In the Potts-Smith procedure, the chest is entered on the side of the arch. The position of the arch is determined by a barium swallow. When the aorta arches to the left, the esophagus is indented on the left, and vice versa.

It must be remembered that congenital pulmonary stenosis may occur in situations other than the tetralogy of Fallot. One of these is tricuspid atresia. In this syndrome, the blood from the right auricle flows through an auricular septal defect into the left auricle, thence to the left ventricle, from which a portion of the blood passes through a defect in the ventricular septum into a diminutive right ventricle, and thence through a hypoplastic pulmonary artery to the lungs. The general clinical picture is similar to that of the tetralogy of Fallot. There are, however, two distinctive features. Roentgenologic and fluoroscopic studies reveal that the right ventricle is diminutive in size. Moreover, the electrocardiogram shows axis deviation to the left.

Dr. Thomas J. Dry, DIFFERENTIAL DIAGNOSIS OF TETRALOGY OF FALLOT:*

The picture of tetralogy of Fallot has been presented very clearly and it has been shown that the diagnosis is usually relatively easy.

In the very young patient the differential diagnosis may, however, be quite difficult because cyanosis, polycythemia, clubbing of the fingers, a basal systolic murmur and right axis deviation in the electrocardiogram are common to many lesions besides the tetralogy of Fallot.

ATRESIA OF THE AORTIC, MITRAL AND TRICUSPID ORIFICES, ABSENT SEPTA AND TRANSPOSITION OF THE GREAT VESSELS

Anomalies such as atresia of the aortic orifice, atresia of the mitral orifice, atresia of the tricuspid orifice, complete transposition of the great vessels and absent cardiac septa are associated with such severe derangements of the circulation that children who have them seldom live more than a few weeks; yet they are not necessarily excluded in older children, for once in a while some amazing examples of longevity occur among persons who have these gross anomalies of the cardiovascular system. The age factor does at least screen out a great proportion of the more primitive types of congenital heart lesions.

TRICUSPID ATRESIA, PERSISTENT ATRIOVENTRICULAR CANAL, COR TRILOCULARE BIATRIATUM

Sometimes an associated finding, either cardiac or extracardiac, may serve as the clue to the correct diagnosis. It has already been pointed out that the occurrence of left axis deviation in the electrocardiogram of a cyanotic child is a significant aid in the recognition of tricuspid atresia. Less pathognomonic, it is true, but of possible diagnostic help is the fact that the most common congenital cardiac anomaly in a mongolian idiot is a persistent atrioventricular canal and that in isolated dextrocardia a trilocular heart is a common finding. The likelihood of a single ventricle (in association with cor triloculare biatriatum) is strengthened when no murmur is audible. This anomaly should not be confused with the tetralogy of Fallot because cardiac enlargement and hilar pulsations usually are visible roentgenoscopically. The electrocardiogram in cases of trilocular heart displays large, biphasic QRS complexes in all leads rather than the outspoken right axis deviation seen in the tetralogy.

PERSISTENT TRUNCUS ARTERIOSUS

Some superficial resemblance to the tetralogy of Fallot, especially in regard to the roentgenographic configuration of the heart, is presented by persistent truncus arteriosus. There is, as in the tetralogy, a loud systolic murmur with an associated thrill (due to the ventricular septal defect which is always present) but the murmur is transmitted into the carotid vessels in addition to being

* From Section on Cardiology, Mayo Clinic, Rochester, Minn.

clearly audible over the base of the heart. However, one can expect to find increased rather than diminished vascular hilar markings and a greater degree of cardiac enlargement than in the tetralogy.

Complete Transposition of the Great Vessels

In those instances in which patients with complete transposition of the great vessels live beyond infancy (such as the case of an 11-year-old child reported by Alexander and White) the lesion can be, and has been, confused with the tetralogy of Fallot. The point of greatest resemblance between the two lesions lies in the upper part of the cardiac shadow. Here the unusual relation between the pulmonary artery (arising from the left ventricle) and the aorta (arising from the right ventricle) is such that the latter is directly in front of the former, with the result that the left upper border of the cardiac shadow is concave as it is in the tetralogy of Fallot. In cases of complete transposition, however, the heart is enlarged, it is globular in shape and otherwise has none of the characteristics of the tetralogy of Fallot.

Eisenmenger Complex

The Eisenmenger complex has much in common with the tetralogy of Fallot, embryologically speaking. In it, as in the tetralogy, a dextroposed aorta overrides a ventricular septal defect and the right ventricle is hypertrophied, but the pulmonary artery is large enough to allow free flow of blood to the lungs. Consequently the cyanosis, dependent largely on the venous blood entering the aorta from the right ventricle, is usually less than in the tetralogy and may not be apparent in the infant. Inasmuch as pulmonary blood flow is unimpeded, exercise is better tolerated than when pulmonary stenosis exists. A systolic murmur is present as a rule, as is right axis deviation in the electrocardiogram but the differential features are again best disclosed by the roentgenographic findings. An enlarged pulmonary conus with exaggerated hilar vascular markings reflecting adequate pulmonary blood flow is a situation which does not exist in the tetralogy of Fallot.

Atypical Tetralogy of Fallot

The crucial feature which characterizes the tetralogy of Fallot is the diminished pulmonary blood flow. There are instances in which the pulmonary artery may be normal in size and yet create a situation functionally similar to the tetralogy of Fallot because its orifice is stenotic. Clinically these cases should be classified as tetralogy of Fallot. Here the cardiac contour is misleading and unless cognizance is taken of other features presented at roentgenoscopic examination, specifically absent hilar pulsations, the diagnosis of Eisenmenger complex could be erroneously made and the patient denied the benefit of surgical treatment. It is in this type of patient that studies of the saturation of hemoglobin with oxygen at rest and during exercise and cardiac catheterization may be of inestimable value.

Dr. Richard J. Bing, Baltimore, Md., The Value of Catheterization of the Heart and Other Physiologic Procedures in the Diagnosis of Congenital Heart Disease:*

Recent advances in the surgery of congenital heart disease have confronted the pediatrician with the necessity of selecting patients for operation. A diagnosis can frequently be made by clinical methods alone. In complex cases, however, physiologic procedures are of help in the recognition of the operable cardiac malformations, which include tetralogy of Fallot, tricuspid stenosis or atresia, and single ventricle with normal or decreased pressure in the pulmonary artery. These conditions have to be separated from the inoperable malformations such as Eisenmenger's complex, partial and complete transposition of the great vessels, and isolated septal defect. The physiologic diagnostic tests consist of catheterization of the heart, measurement of the pulmonary capillary flow, a standard exercise test, and oximetry. It is the purpose of these tests to aid in the recognition of three conditions which have to be present if operation can be attempted. They are (1) septal defect, (2) obstruction to flow in the pulmonary artery with the pulmonary artery pressure below that in the aorta, and (3) reduced oxygen saturation in the peripheral arterial blood.

Catheterization of the heart entails the introduction of a plastic catheter through the antecubital vein into the heart and if possible into the great vessels. During this procedure the catheter is

* From Johns Hopkins Hospital, Baltimore.

moved under fluoroscopic visualization, and blood samples are taken from various parts of the circulation. With the data obtained the volume of blood through various parts of the circulation can be calculated.

The measurement of pulmonary capillary flow or the total pulmonary blood flow is of importance in the recognition of patent ductus arteriosus or large collateral circulation to the lung. The method involves determination of carbon dioxide contents in the respiratory air.

The standard exercise test has as its main objective the recognition of pulmonic stenosis and of intracardiac shunt. The test can be easily performed by children over five years of age and has proved most valuable in the diagnosis of pulmonic stenosis and septal defect.

The oximeter is an instrument which measures the oxygen saturation in the peripheral arterial blood by means of a photoelectric cell attached to the pinna of the ear. Its main value is the continuous registration of the oxygen saturation during the standard exercise test. A fall in the oxygen saturation of peripheral arterial blood indicates the presence of a septal defect.

The results of these tests in tetralogy of Fallot show a reduction of flow in the pulmonary artery and an intracardiac shunt directed from right to left. The systolic pressure in the pulmonary artery is below that in the right ventricle, which is elevated. There is usually evidence of collateral circulation. During the standard exercise test the oxygen consumed per liters of ventilation and the oxygen saturation of peripheral arterial blood decline. In Eisenmenger's complex peripheral arterial blood flow is normal or slightly reduced and the intracardiac shunt may be directed from left to right or from right to left. Hypertension in the pulmonary artery is characteristic of the malformation. During the standard exercise test the oxygen consumed per liters of ventilation rises but the oxygen saturation in the peripheral arteries decreases.

Results obtained with these tests are of aid in the diagnosis of pure pulmonic stenosis, single ventricle with pulmonic stenosis, stenosis or atresia of the tricuspid valve, and isolated septal defect.

Of general physiologic interest is the finding that the basal metabolic rate of cyanotic children is decreased. This represents an important mechanism in the adaptation to the anoxia. The high incidence of pulmonary hypertension in children with congenital heart disease, exclusive of those with pulmonic stenosis, is of significance, since it indicates increased vascular resistance in the pulmonary vascular bed.

Dr. Willis J. Potts, Chicago, Ill., SURGICAL TREATMENT OF CONGENITAL PULMONARY STENOSIS:*

Pulmonary stenosis has become a surgical problem. The critical anoxemia manifested by cyanosis can be relieved by shunting more blood to the lungs. These children, some more—some less cyanotic, are unhappy, sad and dejected. The eyes are suffused, the fingers blue and clubbed. Such a child has something to hope for in the future because of the great pioneer work of Blalock and Taussig and to them belongs all the credit for work on these unfortunate children.

The possibility of performing an aortic-pulmonary anastomosis was considered. If a true ductus arteriosus could be formed there would be no sacrifice of systemic vessels. Furthermore, the opening could be made whatever size seemed proper. However, such an operation could not be done unless blood could be allowed to flow through the aorta while the anastomosis was being made. Complete closure of the aorta in animals leads to paralysis of the hind legs. After considerable work a suitable instrument was perfected which encircles the aorta and pinches off a small portion to which the pulmonary artery is anastomosed.

The principles of the operation were developed on 30 odd dogs with two objectives: to learn the technic of suturing and healing of blood vessels, and the second, to determine the proper size of the anastomotic channel. The proper size was determined on the basis of: first, the size of the patent ductus arteriosus which would not cause too much of a strain on the heart; second, on the basis of the size of the average subclavian artery; and third, on the basis of trial and error. We finally concluded that the proper size of the anastomotic opening was about 4 mm. in diameter.

The first slide shows the pulmonary artery of a dog sacrificed 81 days after operation. You see the rather round clear hole with no sign of thrombus on the edges. The next slide shows the anastomotic channel from the aortic side—silk sutures can be seen beneath the layer of endothelium which has grown over.

Having done this work, the first child presented itself. The youngster was 21 months old and

* From Children's Memorial Hospital, Chicago.

weighed 8.2 kg. and was completely helpless. When she was brought into the admitting room she became unconscious while crying during the examination. We thought probably the time had arrived to try this operation. The mother was fully informed that this operation had never been done on a human being and I particularly show the picture of the mother as well as the child because the mother insisted that the operation be tried. Of such stuff are American women made! The operation was done on September 13, 1946 and on September 13, 1947 she was kind enough to send us this picture. Every one of you have patients for whom you have done something and to whom you have helped to restore health—that is what makes the practice of medicine so much fun.

A few words about the operation. Two factors are essential to good operative results. The first is proper diagnosis, that is, careful selection of those patients who can be benefited by the operation. For this we depend upon Dr. Gibson. The second is anesthesia. There is no operation I know of which requires such consummate skill as that on these youngsters who are living on such a small margin of oxygen safety. One slight error of judgment is sufficient to push them over the edge. All anesthesias have been given by Dr. William O. McQuiston.

The incision is made on the left side if the child has a left aortic arch or on the right side if it has a right arch. Technically the operation is easier on the left side because the pulmonary artery is long. After the pulmonary artery has been isolated the aorta is dissected from its bed. The anastomosis between the aorta and pulmonary artery is made about 1 to 2 cm. below the origin of the subclavian artery. We do not make an anastomosis between the aorta and the main pulmonary artery, of course, but either to the right or left branch. After the clamp is applied it can easily be determined that blood is flowing through the aorta by palpating just below the clamp where a continuous thrill will be felt. Incisions, one-fourth inch long, are made in the aorta and the pulmonary artery and the anastomosis is effected by means of a continuous suture of fine silk. After the anastomosis is completed and the clamp released a thrill will be conveyed to a palpating finger placed over the anastomotic site indicating that blood is rushing through the new opening.

The child is returned to its room and placed in oxygen for a day or two. Penicillin is given routinely for a day or two before operation and for a week postoperatively. The average hospital stay has been 14 days.

Postoperative Complications

These have not been a particular problem; either the child recovers or it dies rather soon following surgery. Four patients in the first 13 cases required aspiration of the chest for removal of the fluid and/or air. Since we routinely put a drain in the chest in the last 50 cases we have had no trouble and no aspirations have been necessary. Six cases had a tracheobronchitis as the result of tracheal anesthesia. Two of these children required tracheotomy, the others recovered after a few days in the steam room.

It is interesting that the suffusion of the eyes which these children have disappears immediately after the operation. The clubbing of the fingers and toes disappears in part during the hospital stay, the rest of it disappears within four to six months.

One youngster six years old, although very blue did not have a high blood count, only seven million, yet she was completely incapacitated. Since without surgery her future was hopeless the parents urged operation realizing the risk that was being taken. While the chest was open her blood was literally black. Following surgery she was completely spastic and unconscious for three days. By the evening of the fourth day she had completely regained consciousness and the spasticity had disappeared. To our surprise she has shown no residual cerebral damage. We can only assume that she had sufficient anoxia of the cerebral cells to produce temporary edema, but not enough to cause final damage.

Mortality statistics are always a matter of interest. I might say that all of the patients upon whom Dr. Gibson made a diagnosis of diminished blood flow to the lungs were operated on regardless of their condition. Seven of these patients had to live in oxygen all or part of the time before surgery. Oddly enough all these seven survived surgery. In the group of 17 from four months to two years of age there were two deaths, a mortality of 12.5%. Five of the children in this group were below one year of age. There were no deaths in the group of children below one year of age. There were two deaths in the two to five-year-old group of 20 or a mortality of 10%. There was one death in the five to 15-year-old group of 25 children or a mortality of 4%. Aortic

pulmonary anastomosis was performed on 61 patients with five deaths or an overall mortality of 8.2%. The causes of death are of interest in these patients. Of the five patients who died, two had cerebral thrombosis, one of which was recurrent. Two died of frank cerebral hemorrhage. The fifth was a misfortune, the child died of a tension pneumothorax.

There is still one other group, the exploratory group. We performed exploratory operations on nine children and four of these children died. Two of them died on the operating table and two died within 24 to 48 hours. At post-mortem examination the findings were identical in all cases. All had pulmonary atresia. All the blood to the lungs was supplied by the bronchial arteries arising directly from the aorta and going to both lungs. These children could not stand the anoxia attendant with opening the chest. One child upon exploration was found to have an Eisenminger's complex not remediable by surgery. The other four children had pulmonary arteries too small to allow a successful anastomosis to be done.

Of those 56 children who survived aortic-pulmonary anastomosis, 54 have excellent results. Two have some residual cyanosis: one, four months old, on crying still becomes cyanotic; the other, six years old, becomes cyanotic when walking fast. In the latter child the murmur is not as marked as it was, the diastolic phase has disappeared and we believe the opening has partially closed. However, the other children are all free of their cyanosis. Their murmurs have persisted, indicating that the newly formed channel is remaining open. Three children have rather marked enlargement of the heart and we feel that they will probably go on to cardiac failure. All children postoperatively have some cardiac enlargement. Approximately 50 children have been restored to comfortable health. We explain to each mother that we cannot correct the pathology in the heart but that we can make the children more comfortable. These children for the most part go to school, they run and play and their mothers are relieved of overwhelming anxiety.

Discussion

Question: What about the use of opaque solution in the diagnosis?

Dr. Bing: Most of the children with uncertain diagnosis were studied by means of intravenous diodrast. The greatest value of angiocardiography consists in the recognition of defects of the venous inflow and in the diagnosis of transposition of the great vessels. However, its value in the recognition of pulmonary stenosis is more limited. The reason for this lies in the fact that the stenosis is frequently infundibular with the result that the opacity of the cardiac chambers is superimposed upon the area of stenosis. Angiocardiography is relatively without danger. One death among several hundred runs was recorded, however. All the patients were tested beforehand as to whether or not they were sensitive to diodrast.

Question: What is the upper age limit for doing these operations for the tetralogy of Fallot?

Dr. Potts: We at the Children's Memorial Hospital have not operated on children above 16. From the statistics and from our findings in older children, I am sure one would prefer to do the operation some time between the ages of two to ten years. We operate on little children below one year of age only because they are going to die if we do not operate on them. In talking with Dr. Blalock I learned that he does not like to operate on patients with pulmonary stenosis above the age of 20 because the mortality in the older group is much higher.

Question: What is the significance of subclavian bruit occurring in otherwise healthy children?

Dr. Dry: I believe that bruit in the subclavian vessels can be heard in a great many normal children. I cannot remember a single one recently in which we demonstrated anything of a pathologic nature. Furthermore, as the children grow older the bruit seems to disappear.

Question: Is position of value in the emergency treatment of the cyanotic heart patient?

Dr. Bing: I think Dr. Taussig made it clear yesterday in her paper that these children as a rule know what position to assume. When they become extremely cyanotic they always assume the squatting position. What good it does it is hard to say. You would think that the oxygen saturation increases but the oxygen saturation actually decreases in some cases. If a child gets an acute attack of cyanosis, I think Dr. Taussig suggests putting him in a knee chest position and giving him morphine. Morphine is more important than any position the child can be made to assume.

Dr. John W. Duckett, Dallas, Tex.: Obviously any further remarks on this subject would be superfluous. You have been listening to the masters in the field. If Drs. Taussig, Blalock and Gross were here, the list would be fairly complete. The clinician, the roentgenologist, the physiologist have

made investigations and have challenged the ingenuity of the surgeons. The surgons have come through with definite advances in this field. Dr. Bing told us this morning that Dr. Blalock has operated on two cases of transposition of the vessels, unsuccessfully, it is true, but indicating that these advances are still going on. Doctor Blalock's brilliant contribution in treatment of the tetralogy of Fallot has been supplemented by Dr. Potts' operation which may prove to be more useful in the very young child. Now the important thing is that these are not simply trick operations that these men have developed. They are fundamentally sound procedures that they have been able to teach others. To name a few, Dr. Clagett at Mayo's, Dr. Humphries in New York, Dr. Barkley in Houston, and here in Dallas myself and my associates as well as many others elsewhere have been enabled to treat congenital cardiovascular disease by their methods.

Round Table Discussion

MANAGEMENT OF INFANTILE DIARRHEA AND DYSENTERY

ANGUS MCBRYDE, M.D., *Chairman, Durham, N.C.*, PHILIP A. MULHERIN, M.D., *Augusta, Ga.*, JEROME S. HARRIS, M.D., *Durham, N.C.*, and DR. ARTHUR H. LONDON, JR., *Durham, N.C.*

Chairman McBryde: Diarrhea is a symptom which may result from many causes. For the sake of simplicity let us state that it may be due to (1) enteric infections, notably the dysentery and salmonella groups, (2) to parenteral infections, and (3) the absence of those factors which result in the relative freedom from severe diarrhea in the private patient group. These factors are proper food, as to quantity, quality, and clean preparation, reasonable clothing, adequate vitamin intake, regularity of schedule, regular advice as to feeding, and the tendency to seek medical advice at an early hour. These factors often do not obtain in the rural and lower economic classes due to ignorance, to lack of cleanliness and to the remoteness or non-availability of medical advice and hospital facilities. I would like to show the following slides concerning the incidence of diarrhea.

Slide #1 is taken from reports of the Bureau of Census and is probably grossly inaccurate. Nevertheless it shows the general trend of infant mortality rates due to diarrhea and enteritis under one year of age in the United States. There has been a steady decrease in the death rate from diarrhea and enteritis under one year of age from a level of 44 per 1000 population in the age group in 1900 to only 4 in 1940. Many of the data here are from estimated figures. The roles played by the development of logical infant feeding with clean milk, education of the public, increased medical knowledge, and availability of medical care need not be commented upon.

The following table shows the infant mortality (death under 1 year per 1000 living births) from diarrhea and enteritis for individual states for the year 1940, exclusive of reported cases of dysentery, and is quite instructive. Lack of proper bacteriologic studies again cloud the data. It can be seen, however, that we are in an appropriate area for the discussion of the management of diarrhea in infancy. The states not listed have mortality rates between 1.2 and 3. Dysentery rates, especially in the southern states are about one-tenth those of diarrhea and enteritis, while in the north few dysentery deaths are reported.

INFANT MORTALITY FROM DIARRHEA AND ENTERITIS FOR EACH STATE
(Deaths under 1 year per 1000 living births, 1940)

Rates 10-15		*Rates 3-6*	
Arizona	14.7	Oklahoma	4
New Mexico	13.5	Tennessee	4
Texas	12.6	Missouri	3.9
Rates 6-10		Virginia	3.7
Colorado	7.1	Mississippi	3.7
Louisiana	6.1	Maryland	3.6
South Carolina	6.1	Wyoming	3.6
Rates 3-6		Florida	3.5
North Carolina	4.9	California	3.3
Arkansas	4.8	Montana	3.1
Georgia	4.5	*Lowest Rates*	
Kentucky	4.4	Oregon	0.8
District of Columbia	4.2	Washington	1.1
Alabama	4.1	Minnesota	1.2

The next slide taken from data of the North Carolina Department of Health shows the average annual figures for the five leading causes of death in white and Negro infants. You will note that prematurity is the leading cause of death while enteritis and dysentery are not so far behind pneu-

From the Annual Meeting of the Academy, Dallas, Tex., December 8-11, 1947.

monia as causes of mortality in the first year. Negroes, who undoubtedly have less available medical care, and less inclination to use that which is available, lead the whites by considerable margins.

When the diarrhea patient confronts one, certain pertinent observations are indicated in evaluating the case and in outlining management. Important facts in this history are (1) the rapidity of onset—rapid onset is more likely to result from bacillary dysentery, (2) the duration which in acute diarrhea often determines the prognosis and the response to therapy, (3) the frequency and size of stools and the character of the stools: large, loose, watery stools are more often associated with marked water and electrolyte loss than are frequent small ones. Inspection and microscopic examination of the stool are essential. Blood and pus cells invariably mean an enteritis, usually dysenteric. More important is the history of prolonged vomiting since the infant often can replace his water and electrolyte by mouth if the fluid intake is adequate. Vomiting, furthermore, means marked reduction in the caloric intake, an important and often neglected factor.

Physical examination is mainly concerned with noting the temperature, the color and general appearance and state of hydration of the infant and with searching for parenteral infections. A high temperature usually means a serious process while dehydration represents a pediatric emergency and always requires hospitalization for adequate therapy.

Mention must be made of the importance of treating mild diarrhea thus preventing severe symptoms. A slight increase in looseness or frequency of the stools calls for immediate measures of treatment. It is our practice in mild diarrhea to omit two or three feedings while substituting 5% sucrose solution in ½ isotonic saline. The child is then placed on diluted unsweetened evaporated milk with or without lactic acid with the sugar-salt solution given as desired between feedings. This is a simple regimen and is adequate in mild non-dysenteric upsets. The addition of 5% casec to 1:2 evaporated milk-water mixtures is also valuable. Solid foods are to be avoided for several days and the less laxative ones, such as pablum or other cereals are added first. If fever is present and if the white blood count is elevated with or without parenteral infection sulfonamides may be indicated. Infants who can take large amounts of fluids orally seldom become dehydrated. If no progress is made and the infant does not improve or becomes worse, especially if vomiting occurs, hospitalization may be required.

Dr. Mulherin: Bacteriologic Considerations: The first slide is from data published by Hardy and Watt and shows the relative importance of bacillary dysentery or Shigellosis. In New Mexico and Georgia 63% of the severe and 33% of the mild diarrheas had positive stool cultures. The percentage increased markedly with the number of cultures taken. The incidence of positive cultures in mild cases varied from 18 to 69%. In the New York area the incidence of positive cultures was somewhat lower. Therefore much information may be obtained from repeated stool cultures. The technic for obtaining the cultures is quite important. The usual routine is to send the stool to the laboratory in the diaper where it may stand for several hours before culturing. When the stool is allowed to stand for any length of time the incidence of positive cultures decreases markedly. The rectal swab technic is by far the best method of obtaining cultures. In infants under six months of age the applicator may simply be inserted in the rectum, turned in each direction and removed. Two plates are then streaked immediately and directly. The original swab is used at the top of the first plate and then discarded and the remainder of the plate is streaked with a fresh swab. The second swab is then used to streak the second plate. In children over six months, obtaining the cultures is more difficult. A rubber catheter, size 24 to 28 French, cut in lengths of about five inches, and bevelled at one end is inserted with the aid of lubricants and through this hollow tube the applicator is pushed into the rectum. It is then moved about and pulled back into the tube, which is then removed from the rectum and the plate streaked. The incidence of positive cultures is also increased by the use of S & S agar (Salmonella-Shigella). Weil has recently divided the common organisms found in this country into two main groups, the Shigella and Salmonella groups. The Shigella organisms are the more common ones in this area though true Shiga is not a problem. Salmonella is a problem only in certain areas. Salmonella is not usually a pathogenic organism for man but is found in many animals and on occasion will infect man at times causing an enteritis.

How are these organisms transmitted from person to person? Most epidemiologic studies have failed to incriminate water, milk or other food except occasionally where carriers are a problem. Many epidemics have occurred in institutions where flies were not present and where the food was handled in a sanitary manner. Cultures of the hands during these epidemics, especially the fingernails, have shown many organisms in individuals suffering from clinical dysentery and those who were symptom free. In private practice a careful history often will reveal that one or more indi-

viduals in the household have had diarrhea prior to the baby's illness—either another child or often an adult. In many cases the adult has attributed the "indigestion" to something he has eaten. Thus personal contact is important in a surprisingly large number of cases.

Thus far we have talked only of bacillary dysentery or Shigellosis. There is, however, a group of diarrheas that occur in early infancy, especially in newborns, about which we have little information but which is extremely important and has often been reported in recent years. These are usually referred to as epidemic diarrhea of the newborn or virus diarrhea. There is some evidence that epidemic diarrhea of the newly-born is a virus disease but we should await further confirmation of the studies already made. However, it is a grave condition and it might be well for us in managing the disease to regard it as a virus disease. Buddingh and Dodd have isolated a virus from the stools of babies with diarrhea, and from mouth swabs of babies, older children and adults with stomatitis, which gives a typical reaction on the cornea of rabbits differing from but somewhat resembling the reaction of herpes.

The following slides taken from the New York State Mortality Records show the deaths from diarrhea under one year of age and under one month of age. You may see that diarrhea under one year of age is decreasing markedly but deaths from diarrhea under one month of age are actually increasing. This is due to the marked increase in the diarrhea of the newborn, so-called virus diarrhea. At the present time it appears that the main method of transmission is by contact from baby to baby or from attendants to the infant.

Dr. T. L. Birnberg, Beverly Hills, Calif.: Do examinations of the stools for bacteria change your treatment much?

Dr. Mulherin: No, because many times you do not get a positive culture but you are still going to treat them. From a practical standpoint it is not too important except to get over the fact that many of the diarrheas we run into are infections—most of them are. I feel personally that if a diarrhea doesn't clear up in about 48 hours, it is probably an infection.

Question: How about blood in the stool—do you regard that as due to infectious diarrhea?

Dr. Mulherin: Yes, but you can have infectious diarrhea without blood in the stool, in fact most of them that we now see are without blood.

Question: And you still think those without blood are mostly enteral infections.

Dr. Mulherin: They have been shown to be—many but not all of them.

Question: At a meeting a number of years ago someone presented a paper reporting that during an epidemic of dysentery cultures of the healthy people in various towns were often positive.

Dr. Mulherin: Yes, they were carriers. Following a clinical illness, the organisms may be carried for as long as 70 to 80 days. As a matter of fact, enteric infections are often transmitted by the carrier. However, the epidemic picture is confused by the large number of strains of related organisms, which can only be distinguished by rather involved agglutination tests, and the relative short period of immunity following an infection.

Question: What about the cause of diarrheas from which no positive cultures are obtained?

Dr. Mulherin: Most of these are enteric infections. Many of you know how you blame a throat that is always pink as the cause of fever, when it probably isn't—I think that we all do this in practice, thus confusing parenteral infections with true enteritis. There is no reason why a child cannot have a mild respiratory infection, and many do, concurrent with infectious diarrhea. And if you take a dozen children with diarrhea in certain seasons of the year you will find one or two with slight infection of the throat. A great number of those (I'm on the virus side largely on this question) from whom you don't culture anything still represent enteral infections. You see many diarrheas that are attributed to parenteral infections in which the diarrhea spreads from one person to another. There is some evidence to show that virus infections which involve the upper respiratory tract are at the same time the cause of diarrhea. This probably is not parenteral infection—I believe this will become increasingly recognized. Diarrheas of unknown etiology on which we cannot get positive cultures are often the most difficult ones to control. This is also true of enteric infections in which are found questionably pathogenic organisms such as Morgan's bacillus.

Question: Do adults and older children react differently from young infants to the same virus? Does not the mortality vary greatly in epidemic diarrhea of early infancy perhaps because of the difference in the character of the virus?

Chairman McBryde: Undoubtedly the young infant is affected differently and more seriously by the so-called virus diarrhea. Apparently the virus does vary in character in different areas. Most of the infants show little at autopsy. They apparently die a "chemical death."

Dr. Harris: In order to administer fluid and electrolyte therapy correctly, it is necessary to understand the changes that have occurred during the development and course of the diarrhea prior to the examination of the patient. The results of both physical and chemical examinations must be evaluated with regard to knowledge of the changes that have previously taken place since these events may be obscured by secondary phenomena. For example, there is a large loss of salt in diarrhea, yet chemical examination of the serum may reveal only a slightly lowered concentration of salt (as measured by sodium). The salt deficit has been obscured by a simultaneous loss of water. Concentrations are thus maintained although the total amounts are markedly diminished. Similarly, there may be a large loss of proteins during the course of diarrhea but examination may reveal hyperproteinemia because of the concomitant dehydration. In the case of potassium, despite the large losses which have been demonstrated by Darrow, the serum levels may be normal or elevated because of the dehydration and renal insufficiency. Rules of therapy based on blood concentrations can therefore by very misleading unless viewed in the light of preceding events and simultaneous changes in body fluid volumes. The clinical impression may likewise be in error. For example, dehydration may be due to deficit in water and be correctable by water alone. More often, however, the dehydration in diarrhea is caused primarily by salt deficiency and is correctable not by water alone but by salt-containing solutions.

Fluid and Electrolyte Balance During Diarrhea

Chart I outlines some of the overall changes which transpire during the course of diarrhea. Together with insufficient intake and absorption, there are excessive losses leading rapidly in more severe cases to large deficits. In the feces, besides water losses, there are increased excretions of extracellular electrolytes, such as sodium and chloride, since the intestinal secretions resemble in

Chart I

FLUID AND ELECTROLYTE BALANCE IN DIARRHEA

1. Insufficient intake and absorption.
2. Water loss in stools, obligatory loss in urine (100-500 ml.) and insensible water loss (0.5-1 ml./kg./hr.)
3. Loss of sodium, chloride, potassium, calcium and magnesium in stools. (Sodium > chloride).
4. Potassium loss due to tissue breakdown, displacement by sodium in muscles, inability of cells to hold K in presence of dehydration and poor circulation. During parenteral saline therapy, additional K may be lost from cells.
5. Excess calcium and phosphate loss due to acidosis.

Protein loss from starvation, tissue breakdown, and through loss of plasma proteins due to dehydration.

Vitamin lack through low intake, faulty absorption, excess utilization and excretion.

composition the extracellular fluids. Generally more sodium is lost than chloride when compared to the relative amounts in blood plasma. Until quite recently, these were the only losses that were seriously considered and our therapy was directed largely toward the replacement of these losses of water, sodium and chloride. The work of Darrow, Rapoport and others has now focused our attention upon other losses (such as those of potassium, phosphate and calcium) which arise primarily from the cells themselves. These deficits had been obscured by our close attention to concentrations of materials in the plasma and our failure to appreciate total quantities as measured by the balance of these materials both during the development of and later during the recovery from the diarrheal state. Large potassium deficits may occur through tissue breakdown with liberation of potassium, through the inability of the cell membrane to hold back potassium in the presence of dehydration and insufficient circulation, and through the displacement of potassium by sodium which normally occurs only in relatively small amounts in the cells. This displacement may be further aggravated by saline therapy. Calcium and phosphate may be lost in the urine because

of acidosis, in addition to the losses in the diarrhea stools. Although it is not pertinent to our topic, I have also included the losses of proteins and vitamins as a reminder that, in very severe and prolonged attacks of diarrhea, it may be necessary to replace these as well as fluids and electrolytes. Other losses, of which we are as yet unaware, undoubtedly occur. We will have to await the results of future balance experiments and of studies of electrolyte and water shifts in the various body compartments to ascertain these changes and alter our therapy accordingly.

Consequences of the Deficits Incurred During Diarrhea

a. *Diminished Fluid Volumes.* The deficits in water and electrolytes incurred during the course of the diarrhea result in contractions of the various body fluid compartments and in an altered pattern (acidosis) of the extracellular fluids. Direct loss of water and salts leads to diminished volume of the blood plasma and interstitial fluid with a tendency towards hyperelectrolytemia, both of which

Chart II

ACIDOSIS IN DIARRHEA

1. Loss of alkaline gastro-intestinal secretions.
2. Accumulation of acid metabolic products due to dehydration and renal insufficiency.
3. Ketosis due to starvation.
4. Failure to burn other acids (lactic) due to dehydration and circulatory failure.
5. Transfer of base from extracellular fluids to cells.

are partially compensated by withdrawal of water from and concentration of the cell fluids. The lowered blood volume leads to circulatory insufficiency and improper functioning of the kidneys. When the condition is advanced, these changes (approaching shock states) must be combatted by the immediate administration of materials designed to increase the blood volume. Notice particularly that, because of blood and protein losses which may be incurred before and during diarrhea, the hematocrit or plasma protein concentration may not be sufficiently elevated to warn of the impending danger.

b. *Acidosis.* The acidosis of diarrhea is based on the causes listed in Chart II. These are largely self-explanatory save for the last item which deals with the possibility that sodium may be lost from the extracellular fluids through transfer to the cells. The potassium, which is replaced by the sodium, would be excreted by the kidneys, and there would be an effective loss of base from the body fluids.

Acidosis so produced calls forth the body defenses against change in pH listed in Chart III. All the mechanisms producing acidosis cause immediate shifts in the blood buffer systems. The bicarbonate buffer system shows a fall in concentration of bicarbonate—approximated by measurement of the carbon dioxide combining capacity. To minimize the result of this change in bicarbonate concentration, the lungs, by over-ventilation, lower the carbonic acid content of the blood while the kidneys excrete acid and conserve base. These mechanisms may be used as guides for therapy

Chart III

DEFENSE AGAINST CHANGE IN pH

1. Action of blood buffer systems
2. Respiratory compensation
3. Action of kidney
   a. Variation in concentration (1.002-1.045).
   b. Variation in pH (4.8-8.0) with direct excretion of weak acids or bicarbonate.
   c. Differential excretion of acids and bases.
   d. Manufacture of ammonium ions (limit of 390 mEq/day or 33 gm. $NaHCO_3$).
4. Transfer of sodium to and from cells (?)

since hyper-ventilation ordinarily does not become clinically evident until the carbon dioxide combining power has fallen to 16 mEq./l. However, the respiratory mechanism may fail in cases of very marked dehydration and in very young or premature infants. Instead of hyperpnea, one may see irregular or only slightly altered breathing which fails to compensate and also fails to give the impression of acidosis even though the patient is in urgent need of corrective measures. In order for the kidney to function against changes in pH, it requires at least an adequate circulation, water, and salts. In states of severe water and salt deficiency accompanying diarrhea, the function of the kidney is limited and retention of metabolites may serve to increase the acidosis. As a result of renal insufficiency, one cannot rely entirely on its ability to correct either dehydration or acidosis when supplied with water and salt as one may do when the condition is not as severe. For example, administration of physiological saline may temporarily increase the acidosis since the kidney cannot excrete a sufficient excess of chloride over sodium. This will be explained more fully later.

Design of Therapy

Parenteral therapy will usually be necessary to compensate for those acute alterations which endanger life and to supply maintenance requirements until the patient can take fluids orally without vomiting or having an exacerbation of the diarrhea. At that time, clear fluids may be given by mouth to be followed, if all goes well, by ordinary fluids and then a soft diet. I would like to emphasize the fact that all infants with diarrhea do not need the treatment for the severer cases which I will outline. The milder cases may be started, after a short starvation period, with the clear fluid regimen or even with a mere restriction in caloric intake.

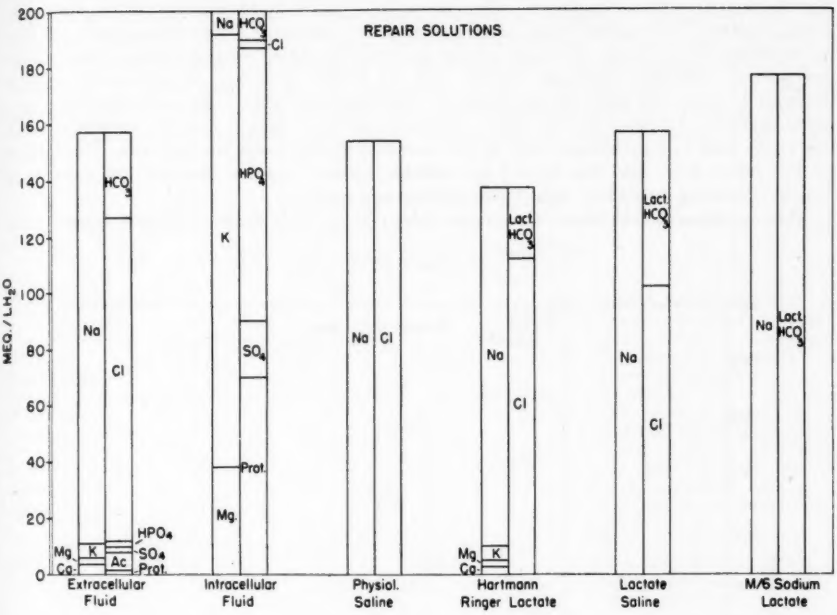
In severe diarrhea, the immediate therapy must be designed to correct (a) the diminished extracellular fluid volume and resulting circulatory impairment (shock), (b) water and electrolyte deficits in both extracellular and intracellular fluids, (c) renal insufficiency and azotemia, (d) acidosis and ketosis. It is my impression that the salt deficiency with resulting lowered extracellular volumes is far more important than the acidosis although the latter has received more emphasis both in teaching and in the literature.

(A) *Fluid and Extracellular Electrolyte Correction.* In order to correct the diminished volume of the body fluid compartments, particularly the lowered plasma volume, and to supply the extracellular electrolyte, it is necessary to give saline containing fluids in amounts of 40 to 100 ml./kg. body weight. The amounts required can be given only in rough approximation since they vary with the extent of the water and salt deficit. The best rule is to give sufficient quantities to establish and maintain an adequate urinary volume containing appreciable salt. If shock is present, plasma or blood in amounts of 10 to 20 ml./kg. may also be necessary in order to rapidly restore the blood volume and prevent further circulatory impairment.

The saline containing fluids usually administered are depicted in Chart IV, along with the composition of the extracellular and intracellular fluids. The type of diagram and the figures for the body fluids stem from Gamble. The concentration of each electrolyte is given in terms of electrochemical equivalents by the height of the corresponding column—a method of presentation necessitated by the fact that the body handles the electrolytes in electrochemical equivalents rather than in terms of weight or volume. Extracellular electrolyte consists largely of sodium chloride and bicarbonate in a ratio of approximately six ions of sodium for every four ions of chloride and one of bicarbonate. Notice the physiologic (isotonic) sodium chloride solution does not show this ratio—there are equal numbers of sodium and chloride ions. When isotonic saline is given to correct dehydration, there are equal numbers of sodium and chloride ions. When isotonic saline is given to correct dehydration, chloride is given in excess of sodium as compared to their relative amounts in normal plasma. The relatively greater increase in chloride ions may aggravate a pre-existing acidosis—particularly if there is renal insufficiency and the kidney is unable to excrete rapidly the excess chloride ions.

To obviate these difficulties, solutions have been designed with compositions more closely approaching the pattern seen in the extracellular fluids. Hartmann's Ringer's-lactate solution (obtainable commercially in concentrated form) has a pattern similar to plasma since the lactate present is converted by the body to bicarbonate (as indicated in the diagrams). Lactate saline solution is frequently used since the slight excess of potential alkali tends to correct the acidosis of diarrhea while the saline portion supplies the needs for water and salt. This solution is composed of two parts of physiologic saline and one part of M/6 sodium lactate. All three types of fluids may be

CHART IV



given intravenously or subcutaneously—depending upon the volume and speed of administration required.

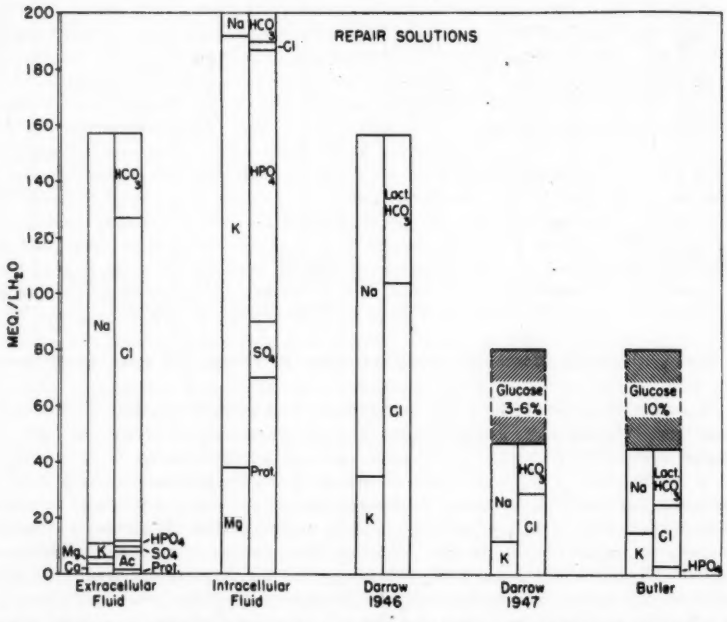
(B) *Acidosis.* The above solutions will automatically tend to correct acidosis since they furnish the kidney with sufficient water and electrolyte to allow adequate renal defense and repair of the extracellular fluids. The base sparing and acid excreting mechanisms can function and excess chloride is excreted relative to the excretion of sodium. The extra sodium remaining in the body will react with carbonic acid, increasing the bicarbonate concentration (carbon dioxide combining power) and raising the pH. The solutions will be more effective if glucose is administered simultaneously to combat the ketosis. In this event, the solutions may be given subcutaneously if mixed with 5% glucose rather than 10%. A hypotonic salt mixture of two parts of saline solutions with one part 5% glucose is actually preferable to the isotonic saline solutions because of the renal insufficiency which may be present. As Moyer has so well illustrated in surgical patients, a lowered concentrating ability of the kidney may make it unable to retain sufficient water from isotonic saline for the body needs—a situation somewhat analogous to the drinking of sea water by a normal individual. Typotonic saline solutions solve this problem.

The advantage of this method for correcting acidosis is that there is no danger of over-correction. The cerebral hemispheres of the physician are far inferior to whatever mechanisms control a relatively normal kidney in the regulation of the body fluids. On the other hand ,the method is very slow and suitable primarily for the milder acidotic. When acidosis threatens life, it is necessary to resort to more rapid means of correction and directly administer alkali or substances, such as sodium lactate, which are rapidly converted to alkali by the metabolism of the body. M/6 sodium lactate solutions (Chart IV) may be given intravenously or subcutaneously in the amounts listed in Chart VII. The result is theoretically the same as the slow administration of 1.4% sodium bicarbonate in a 1.5% glucose solution since the lactate is burned to bicarbonate by the body. The conversion is indicated in the charts by the bicarbonate symbol under the lactate. Sodium bicarbonate may be administered directly (by intravenous route only) for more rapid correction. These solutions correct the acidosis much more rapidly than saline since they do not rely upon the kidney for their

effect. On the other hand, the more rapid the action the greater is the danger of over-correction. My personal preference is to combine the two methods so as to retain the advantages of each. For the severely acidotic, I prefer to correct the acidosis rapidly by M/6 sodium lactate until it no longer threatens life (one-half of the amount calculated to completely correct the acidosis) and then to administer the hypotonic saline and glucose solutions for slower renal correction of the remaining acidosis. Naturally, continuing diarrhea with the further production of acidosis may make it necessary to repeat the procedure. Although we have only very vague ideas concerning the adjustments necessary, I believe that the slower correction (after the danger of severe acidosis is past) allows the body to accommodate better to the changes occurring during the correction. The dangers of the post-acidotic state (see below) are probably lessened and one does not run the risk of suddenly throwing an acidotic patient into alkalosis and tetany.

These solutions should correct the volume deficits of the body fluids, circulatory failure, renal

CHART V



insufficiency, ketosis, acidosis and some of the extracellular electrolyte deficits. It should be stressed that all of these solutions may be given by mouth in the milder diarrheas and whenever oral intake does not produce vomiting or increased diarrhea.

(C) *Intracellular Deficits.* The compositions of the solutions thus far mentioned resemble that of the extracellular fluid and do not contain materials present in large amounts in the cells or bones such as potassium or calcium.

Potassium: The deficit in potassium has been intensively studied by Darrow who states that as much as ¼ to ½ of the total muscle potassium may be lost. Darrow and Butler have devised solutions designed to correct both the extracellular losses, the acidosis and also to furnish potassium for the intracellular fluids. (Chart V). Fluid is supplied for the dehydration, sodium and chloride for the extracellular electrolyte deficit, lactate or bicarbonate for the acidosis, potassium for the intracellular deficit, glucose for the ketosis and, in Butler's, there is some phosphate for cellular replacement. The composition and tentative rules for administration of these fluids are given in Chart VI. You will note, however, that the first solution (Darrow 1946) contains some seven times as much potassium ion as is present in extracellular fluids (blood plasma) though the amount is

small compared to the concentration within the cells. Potassium is very toxic when present in excess in the extracellular fluids and a rise in plasma potassium concentration causes symptoms referable to the heart, nervous system and muscular system (changes in T waves, heart block and muscular weakness). Doubling the serum potassium concentration may precipitate severe and fatal reactions. Intravenous administration of potassium containing solutions may thus cause reactions because (a) the serum potassium may be high initially in spite of the total deficit, (b) the solutions may be given too rapidly, so that the administered potassium accumulates in the extracellular fluids before it can be either transferred to the cells or excreted into the urine. One should therefore first

CHART VI

ELECTROLYTE REPAIR SOLUTIONS

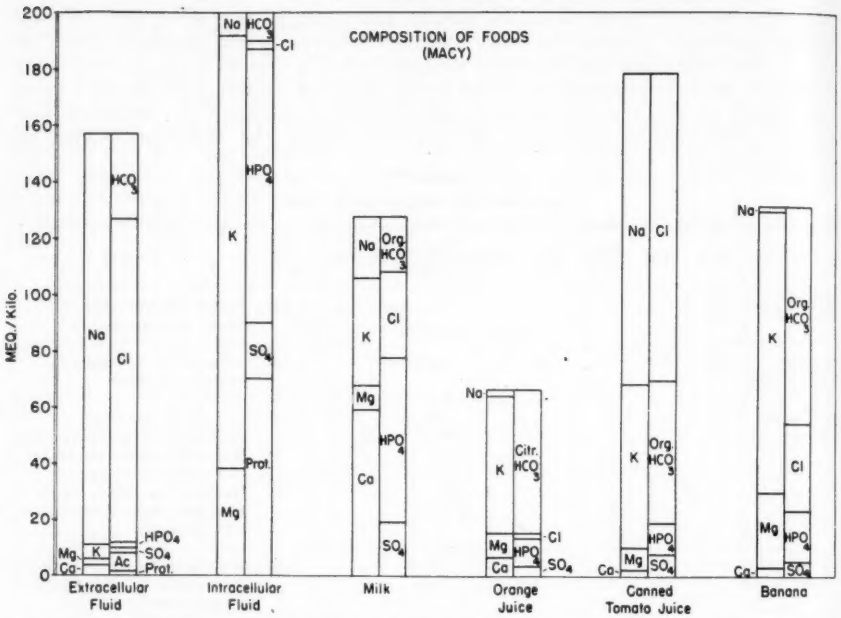
Solution	NaCl	KCl	$CaCl_2$ $2H_2O$	$MgCl_2$ $2H_2O$	$NaHCO_3$	M. Sod. Lactate	K_2HPO_4	Water Q.S.	Remarks
Physiol. Saline	9.0							1,000	1-2 parts may be mixed with 1 part 5–10% glucose
Hartmann Ringer Lactate	6.0	0.4	0.2	0.2		25 ml.		1,000	1–2 parts may be mixed with 1 part 5–10% glucose.
M/6 Sodium Lactate						167 ml.		1,000	60 cc. (45–65) per kg. for 30–35 vols. percent $BHCO_3$ deficit. May be mixed wth 2 pts. saline.
Isotonic Sod. Bicarb.					15.0			1,000	Intravenous only. 55 cc./kg. for 30–35 vols. percent deficit = 17 ml. of 5% solution.
Darrow* 1946	3.0	2.0				40 ml.		750	80 cc./kg./24 hrs. Then 150 ml. per kg. of mixture 1 part to 2 parts of 5% glucose per day.
Darrow* 1947	3.0	2.7			4.4			1,000	Mix 1 part to 2 parts 5–10% glucose given as above.
Butler*	0.58	0.89				20 ml.	0.25	1,000 10% gluc.	150–200 ml./kg. at rate of 0.8 ml./min. for infants per day.

* *Important:* All solutions containing potassium (over 4 mEq./L) must not be given until *after* therapy for circulatory collapse, dehydration and renal insufficiency. Precede potassium solutions by glucose and saline (15 cc./kg.) plus 10–20 ml./kg. blood or plasma as necessary.

correct the dehydration with non-potassium containing solutions in order to start adequate urinary excretion and then give the potassium solutions very slowly. To lessen the dangers Butler has devised the solution shown in Chart V. It is hypotonic in electrolyte concentration (see above), contains glucose and a much smaller amount of potassium. Potassium intoxication is less likely to occur but the same precautions of slow injection and previous hydration must be observed. Subcutaneous injection of Darrow's 1946 solution or the other solutions in 3% glucose (since the electrolyte concentration is circa 30% isotonic) is safer because of the slower absorption.

Calcium: Rapoport has recently stressed the importance of calcium in diarrheal states. During the course of the diarrhea, much calcium may be lost but the ionized calcium content of the blood (upon which neuromuscular irritability depends) may be relatively normal because of renal insufficiency and the increased ionization of the calcium during acidosis. However, the ionized calcium level may drop sharply as soon as renal function is restored and the acidosis has been corrected. At this time, the immediate "post-acidotic" period, a rapid transfer of calcium (and also potassium and phosphate) may take place to the cells and bones depleted of these materials during the "acidotic" phase of diarrhea. The symptoms, as pointed out by Rapoport and his coworkers, include not only convulsions and carpo-pedal spasms but also ocular, autonomic system, temperature regulating, hydration and hemorrhagic manifestations. Immediate therapy consists of the intravenous injection of 0.5 to 1.0 gm. of calcium gluconate (as 2% solution) or calcium chloride (as 1% solution). Measures to prevent the development of the post acidotic state and for maintenance after the control

CHART VII



of the acute symptoms consist of the oral administration of 1 to 3 gm. of chloride (diluted to 2% in the formula) or of gluconate. Rapoport advises that these measures be instituted as soon as the acidosis has been controlled and oral fluids started.

It is rather interesting to note the composition of some of the foods which are used early in the treatment of diarrhea. On Chart VII, I have depicted their composition (from Macy) in the Gamble method. Milk (preferably boiled and skimmed) contains excellent amounts of necessary electrolytes in good proportion. Both orange juice and canned tomato juice (salted) contain large amounts of potassium. I was also struck by the fact that, of the solid foods used in diarrheal states, the banana has about the highest concentration of potassium. Perhaps its usefulness in chronic diarrheas could be in part related to this fact.

SUMMARY OF THERAPY

Severe diarrhea with vomiting demands cessation of food and fluids orally. The next step is to combat the shock, low blood volume and renal insufficiency which may be present. All patients with dehydration and electrolyte deficiency will, even though shock is not present, show a marked predisposition towards shock. Both may be combatted by the use of plasma or whole blood in amounts of 10 to 20 ml./kg. body weight and by the administration of the extracellular type fluids such as Hartmann's Ringer's-lactate in amounts of 10 to 40 ml./kg. body weight. If shock and circulatory collapse are not present, the administration of the Ringer's-lactate solution will tend to restore blood volume and minimize the danger of shock. Following this, one should direct attention to the acidosis, ketosis and remaining deficits in fluid and electrolyte. If the acidosis is severe, it may be rapidly corrected by sodium bicarbonate solution intravenously or by Hartmann's M/6 sodium lactate solutions intravenously or subcutaneously. The amount administered should be sufficient to raise the carbon dioxide combining power to roughly ⅔ of the normal (circa 18 mEq./l.). One can use rough clinical guides for estimation—ordinarily hyperpnea becomes evident at carbon dioxide combining powers below 16 mEq./l. while severe clinical manifestations of acidosis are present at combining powers below 9 mEq./l. If the acidosis and ketosis are mild and not threatening life they may be corrected by any of the hypotonic saline solutions containing lactate or bicarbonate such

as the Ringer's-lactate or lactate saline mixed with ½ to 1 part of 5% glucose. The glucose also serves to prevent some loss of proteins and electrolytes as Gamble has so well demonstrated. Rules for the amounts to be given are of little value. Ordinarily the infant will need a total intake the first day of 40 to 100 ml./kg. for replacement and 100 to 150 ml. for maintenance. The best rule, however, is to give that amount of fluid which will establish and maintain an adequate urinary output.

Once urinary output is established, the remainder of the electrolyte deficits in the extracellular fluids may be corrected by the potassium containing hypotonic solutions of Darrow or Butler in the amounts indicated in the chart. At the same time, these furnish some intracellular materials for deficits in the latter compartment. This is not yet recommended as a routine procedure because of the dangers attendant on their administration and because, although deficits in potassium have been shown to occur in diarrhea, there is no proof that potassium decreases the mortality in diarrhea. Adequately controlled studies on this point are as yet lacking.

The therapy thus far outlined should largely correct the acidosis, ketosis, dehydration and salt deficiency. At this time, the patient should be watched for the dangers of hypocalcemia in the post-acidotic phase and, if necessary, given the calcium therapy mentioned above. It is also wise to pay attention to possible losses of the vitamins. Patients with long standing or severe diarrhea may show some vitamin K deficit and certainly may have other vitamin deficiencies whose effects have not been demonstrated as clearly.

If the patient is still unable to take fluids by mouth, maintenance therapy must be continued parenterally. Usually this will consist of hypotonic saline solutions with glucose in amounts of 100 to 250 ml./kg. depending upon the severity of the diarrhea. If parenteral feeding is necessary for a prolonged period, amino acids should be administered. Parenteral alimentation has been well reviewed by Butler and Talbot and is not pertinent to the present topic.

Dr. London will discuss the institution of oral feeding for the milder patient and for the severe case after the parenteral corrective measures have been successful. Potassium chloride (1 to 2 gm. daily) and well diluted calcium salts may be added to the daily formula in order to be certain that the potassium and calcium requirements have been met. The fluids and foods he will mention provide adequately for the fluid and electrolyte requirements.

Dangers in Fluid and Electrolyte Therapy

In summary, I should like to point out some of the pitfalls in therapy (Chart VIII). The first is the failure to correct shock. One hesitates to give plasma or blood to a patient who has a high

Chart VIII

DANGERS IN ELECTROLYTE AND FLUID THERAPY

1. Failure to correct shock because of hemoconcentration.
2. Early use of subcutaneous glucose which immobilizes fluid and causes further electrolyte deficiency.
3. Alkalosis and tetany from excessive alkali.
4. Edema, potassium loss and increased acidosis from excessive saline.
5. Potassium intoxication from rapid or excessive K therapy—especially in dehydrated states.
6. Post-acidotic state—excessive deposition of K, HPO_4 and Ca in tissues with fall in serum values.
7. Intoxication or sloughing from calcium therapy.
8. Hypoglycemia on stopping long continued intravenous glucose therapy.

serum protein concentration or a high hematocrit. Nevertheless a shock-like state may exist wherein the deficiency in both plasma and blood are obscured by the dehydration and diminution in blood volume. Conversely, a normal hematocrit and normal level of serum proteins may not indicate normal conditions because an anemia and hypoproteinemia may actually be present and revealed only after hydration. The clinical impression of circulatory insufficiency (low blood pressure, vascular collapse and shock) is far more important in determining the need for therapy.

Secondly, the early use of subcutaneous glucose may exaggerate the electrolyte deficits since the salts of the extracellular fluids will diffuse into a depot of subcutaneous glucose before absorption of the fluid can take place. Experimentally, salt deficiency in animals has been produced in similar fashion by giving large amounts of isotonic glucose intraperitoneally and withdrawing the same amount of fluid after a short interval. There is no volume change under these conditions but the body salt which has diffused into the glucose solution is removed.

Third, excessive alkali therapy may result in alkalosis and the manifestations of tetany. The latter is more likely to occur in infants who have lost large amounts of calcium during prolonged diarrheas and who are thus predisposed to the dangers of the postacidotic state. The use of excessive amounts of physiologic saline has several dangers. It may cause edema, produce additional potassium loss through replacement of potassium by sodium in the muscles and also increase the extent of the acidosis because of the non-physiologic proportions of sodium and chloride. Lastly, it may cause an excessive concentration of electrolytes in the extracellular fluids with continued intracellular dehydration if kidney function is sufficiently impaired. The isotonic saline then has the effect of hypertonic saline because of the continued insensible losses of relatively salt-free water through the lungs and skin. Unless the kidney can concentrate the saline sufficiently to "free" water for the insensible losses, the injected saline will becom "hypertonic."

Potassium intoxication may occur from rapid or excessive administration of solutions containing higher concentrations of potassium than in plasma—particularly in dehydrated states where diffusion of potassium into the tissues and urine may be delayed. Dangers are also attendant upon the failure to recognize the postacidotic state and from therapy with calcium. Lastly, one may see hypoglycemia rarely on suddenly stopping long continued intravenous glucose therapy.

Discussion

Question: Will you discuss the use of amino acids?

Dr. Harris: Ordinarily, although the excessive losses and utilization of proteins in diarrhea are recognized, protein therapy is not critical because of the relatively short duration of the illness before oral intake of foods is instituted. However, if the diarrhea is prolonged, replacement therapy is necessary. The patient should receive at least the minimum maintenance requirement of 1 to 2 gm./kg. body weight/day of protein (as amino acids). Amino acids are theoretically equivalent on a weight basis with proteins. We usually give it in the form of a 3½% solution made up of ⅓ 10% glucose, ⅓ 10% amino acid solution and ⅓ saline. One of the companies dispenses such a mixture for parenteral use. Amino acids may be given by mouth if the infant will take it without vomiting or increased diarrhea.

Question: What comment would you make on the German practice of keeping the children on tea diets for a long time?

Dr. Harris: The patients would get very little from that save for fluids. Actually, some harm may be done. Diarrheal patients have electrolyte (salt) deficiency. The administration of tea or water cannot replenish the salt and may force the excretion of additional salt through kidneys which may be unable to conserve salt adequately. The net result is a further loss of salt which entails an additional loss of water and increased extracellular dehydration. Salt deficiency and dehydration may be produced in a similar fashion in experimental animals. Further, if large amounts of tea or water are forced in salt depleted individuals, water intoxication may ensue.

Question: Do you feel that fluids should always be given intravenously rather than subcutaneously?

Dr. Harris: The mode of administration of the fluids depends upon the state of the patient, the fluid to be given, and the amount necessary. If the child is severely dehydrated and in critical danger because of circulatory collapse, I believe that fluids must be given intravenously. Under these circumstances, circulatory impairment makes absorption from subcutaneous depots even slower than normal. Death may occur before correction can take place. After that stage and also for maintenance therapy, most of the fluids may be given subcutaneously. Isotonic saline, Hartmann's Ringer's-lactate and lactate saline solutions may be given subcutaneously either plain or mixed with ½ to 1 part of 5% glucose. M/6 sodium lactate but *not* sodium bicarbonate may also be given subcutaneously. The isotonic solution of Darrow 1946, either plain or mixed with 5% glucose, is actually safer to give subcutaneously because of the slower absorption and the lessened danger of potassium intoxication. The hypotonic potassium solutions of Butler and Darrow can also be given subcutaneously if made up in 3% glucose. The route of administration is also determined by the amount to be given daily.

If the oral route is contraindicated, a constant intravenous drip is probably the best way to ensure complete maintenance therapy (see Butler and Talbot).

Question: I notice that none of the participants in this discussion have mentioned a classification of diarrhea (such as the Finklestein). Can you treat these patients without such a classification? Another thing—granted that it is best to get these diarrhea patients into a hospital so that parenteral fluids can be given, what can you do about them at home? This is a serious practical point in the majority of patients.

Dr. Harris: Most of the older clasisfications of diarrhea merely put into arbitrary categories what was essentially a continuous disease from the most severe (toxicosis or cholera infantum) to the most mild (dyspepsia). Except for the classifications which differentiate between the causes of diarrhea (such as parenteral or dysentery, etc.), I do not believe them to be of any assistance.

Whether one can treat these patients at home depends upon the severity of the process. It is doubtful whether the fulminating cases showing evidence of rapid circulatory collapse can be treated successfully save by hospitalization and vigorous, well designed therapy. On the other hand, the moderately or mildly ill diarrhea patients are frequently overtreated by parenteral therapy when it is not necessary. The parenteral route has no advantage over the oral unless the latter causes vomiting or an increase in diarrhea. In patients that respond to a short period of starvation the same solutions advised for parenteral therapy may be given by mouth. Frequently infants will take large amounts of hypotonic saline sweetened with sucrose or glucose even more readily than they will take plain water or glucose solutions. It is actually preferable to give potassium containing solutions orally, whenever possible, because toxicity is thus avoided. If the patient can tolerate foods (such as boiled skim milk or diluted juices), these may be started in small amounts and increased. Chung and Holt have shown that, even though oral feeding may increase the diarrhea, the material absorbed is greater than the increased excretion so that a positive balance results. Although I do not agree with the implications that feedings should be instituted in spite of an increased diarrhea, such work emphasizes the possibility that we may be using parenteral therapy more often than is necessary.

Dr. London, Jr.: Most of you remember the time when the treatment of diarrhea consisted principally of changes in diet and the use of non-specific therapy, such as, bismuth, paregoric, and chalk mixture, scraped apple and apple powder, banana powder and mashed bananas. With the introduction of sulfonamides, there has been a change in our outlook on the therapy of diarrheas. There was an immediate drop in the hospital population of diarrhea, due to the fact that so many of these cases responded to treatment in the home; and, instead of having wards filled with diarrhea in the summertime, this disease became one of the less common causes for admission to the hospital. You know, of course, the first sulfonamide introduced was sulfanilamide—the first one widely used in diarrhea was sulfathiazole. These preparations were followed by the introduction of sulfadiazine, sulfamerazine and sulfasuxidine. Later, penicillin and streptomycin were introduced and both of these are effective in certain types of diarrhea. The commonest drug used is one of the sulfonamide preparations. In the use of these preparations you have a decision to make as to whether to use a soluble or an insoluble form. In those cases of diarrhea in which the infection is due to the dysentery group of organisms, either sulfadiazine or sulfasuxidine is effective. If the case is where it can be closely observed, the soluble preparation may be used in the home; but where observation cannot be close, it is probably preferable to use the non-soluble form, since the possibility of complications with this are less than with the soluble preparations. We feel that, in the mild cases, that are being treated at home, sulfasuxidine is preferable. If the child is more seriously ill or if there is question of parenteral infection, the soluble preparation, sulfadiazine, is to be preferred. In those cases where the organism is not affected by sulfonamides, certain cases will respond to penicillin or to streptomycin. As the slides show, the various organisms, which from time to time have been incriminated in various types of diarrhea, are dysentery, salmonella, streptococcus, typhoid. There has been some evidence to show that a colon bacillus is occasionally pathogenic and that this bacillus is not differentiated by cultural characteristics but by immunological reactions.

In addition to specific antibiotics, we like to use kaolin preparations which seem to give the child some definite comfort and probably has a salutory effect on the diarrhea. In addition to this, it gives the parents something to do in carrying out orders and keeps them too busy to carry out the suggestions of either the family or the well-intentioned neighbors. We usually use a kaolin-pectin mixture and suggest that the mother give the child a teaspoonful every time the child's

bowels move. An additional advantage in this medication is that the mother usually gives water to help wash down the medicine and this increases the fluid intake of the child.

In some cases of staphylococcus and streptococcus infections, particularly when the child is vomiting and we are not able to administer sulfonamides as desired, penicillin may be used. In some of the diarrheas due to the salmonella group of organisms, steptomycin in large doses may be effective. The suggested dose is 1 to 3 gm. a day and it is important to remember that it should be given early. If small doses are used the organisms may rapidly develop a resistance to the drug. There has been recently reported a group of very severe enteral infections due to pyocyaneus and in these streptomycin, parenterally and by mouth is specific. A total of 3 gm. per day was given—about 400 mg. by mouth every four hours. These cases, if recognized and treated early, may survive.

Question: Have you ever tried apple treatment in diarrhea for children?

Dr. London: Yes, we have. A certain group of parents are very cooperative in using the apple treatment. If there are older people around who still remember the days when most summer diarrheas were attributed to indigestible foods, particularly to eating green apples, you will find difficulty in getting cooperation. However, prior to the use of sulfonamides, the apple treatment certainly enjoyed a good reputation and gave good results by comparison with other methods that we had to use. Bananas, too, have been used extensively and with good results.

Question: What dose of sulfonamide do you use?

Dr. London: The insoluble preparation we use is sulfasuxadine, 0.3gm./kg. body weight/day. The first dose is also 0.3/kg. I believe that the mistake in using the insoluble preparations is that a great many cases are given too small a dose, particularly the initial dose.

In summary, it is our practice in those cases which do not appear extremely ill and can probably recover at home to use the insoluble preparations because of the fear of possible kidney blockage resulting from lack of fluid intake. Those cases that appear extremely ill are placed on a soluble preparation and admitted to the hospital where the fluid intake can be properly checked and the danger of kidney blockage obviated. Also, in those cases of diarrhea which accompany obvious parenteral infections, we use soluble preparations with the idea of clearing the parenteral infection and thus correcting the diarrhea.

Question: Have you any experience with buttermilk?

Chairman McBryde: Either cultured or chemical lactic acid milk, including buttermilk is of value in treating diarrhea patients as it is well tolerated as an initial food. It is perhaps of greatest value as a routine feeding in preventing enteritis by preventing contamination of milk. We seldom if ever have a dysenteric patient who has been on lactic acid milk admitted to our wards.

To return to chemo-therapy, it is interesting to speculate on the mode of action of sulfonamides in dysentery. Many observers believe that the large doses of non-soluble sulfonamides are necessary not because of the bowel concentration achieved but because the large doses result in some drug being absorbed and utilized. Hardy and his group found that the soluble sulfonamides are more efficacious and felt that the bowel concentration was secondary. In a group of 1500 adults followed by cultures the order of effectiveness was (1) sulfadiazine and sulfapyrazine, (2) sulfasuxidine, (3) sulfamerizine, (4) sulfathiazole, (5) sulfamethazine, (6) sulfaguanadine and (7) sulfapyridine and sulfacetimide. It is our practice to use sulfadiazine as we feel that a child who cannot take sufficient fluids to allow proper excretion of the drug should be hospitalized. Also in many cases where parenteral infection may play a part sulfadiazine is more valuable. In typical dysentery when the patient cannot be followed the less soluble forms certainly should be used.

Pediatrics

VOLUME 2 SEPTEMBER 1948 NUMBER 3

SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

EDWARDS A. PARK, M.D., *Editor,* AND PAUL HARPER, M.D., *Associate*

INTRODUCTION

TWO letters are presented which take opposing views of federal aid for medical education and for pediatric education in particular.

The first of these is from Alan Valentine, LL.D., President, University of Rochester, N.Y. Dr. Valentine read a paper on the financing of the privately endowed medical schools before the 1948 Annual Congress on Medical Education and Licensure. (J.A.M.A. 137:1, 1948.) He is eminently qualified to discuss this subject. His extraordinarily able and realistic presentation of the current and future financial needs of medical schools concludes with an answer to the contrary view of Dr. William C. Black. (PEDIATRICS 1:561, April, 1948.)

The second letter is from Dr. Thomas O. Gamble, Professor of Obstetrics, Albany Medical College, Albany, N.Y. Certain aspects of Dr. Gamble's letter require comment. In his third paragraph, Dr. Gamble quotes incompletely from the ICH Committee Report (PEDIATRICS 1:524, 1948) as follows: "It was finally agreed (Ed. note: i.e., by the ICH Committee) that neither the U. S. Children's Bureau nor the U. S. Public Health Service should be the administrative agency, but that the matter should be determined by the Federal Security Administrator, *whose agency includes both the U. S. Children's Bureau and the U. S. Public Health Service.** The correct quotation is: "It was finally agreed that neither the U. S. Children's Bureau nor the U. S. Public Health Service should be *named*† the administrative agency . . . (etc.)." The position of the ICH Committee was and is that the Federal Security Agency, which already administers grants-in-aid for study and training in several fields of medicine, would be the logical administrative agency; it was not considered within the province of the ICH Committee to recommend which branch of this agency should be designated by the administrator. There was no attempt at "camouflage," as suggested by Dr. Gamble.

Dr. Gamble next attacks the recommended composition of the Council on Pediatric Education. He suggests that the Academy should say to the Federal Security Administrator: " 'Mr. Ewing, here are nine names; you appoint them, or the deal is off.' " It is well to remind ourselves that the proposal of the ICH Committee is for more pediatric training

* Dr. Gamble's italics.

† Editor's italics. This is the word omitted in Dr. Gamble's quotation.

for all interested physicians, particularly for general practitioners; and not merely for more training for pediatricians. The proposed council should represent these other physicians, as well as the members of the Academy, and should also represent the medical schools. Dr. Gamble is correct that the recommendation regarding the Council might well be strengthened, but not by having the American Academy of Pediatrics dictate the entire composition of an advisory Council which is intended to represent all interested medical groups.

It should be noted that the letters of Dr. William C. Black and Dr. Thomas O. Gamble are the only ones which have been received for publication in opposition to the recommendation of the ICH Committee. It is felt that the case for the opposition has not been adequately stated. The editors of this column are desirous of presenting fully all sides of this question, and will consider for publication any communications.

PAUL HARPER

June 21, 1948

MY DEAR DR. PARK:

I address this letter to you as an editor of PEDIATRICS because of my interest in medical education (including pediatrics) and its future financing, and because an acquaintance has let me read a copy of a letter addressed to the members of the American Academy of Pediatrics, dated March 19, 1948, and signed by William C. Black, M.D.

Dr. Black's letter seems to me so one-sided and emotional a document that I fear the harm it may do to the future cause of pediatrics and to medical education in general, and am therefore moved to reply. It takes courage to do this, as I am not a medical man and therefore am perhaps disqualified in the opinion of medical men from offering opinions on this subject. But I am deeply concerned with medical education and its future welfare, and in some small degree responsible for it in connection with a rather important medical school. What is more, since medical education and medical care are of the utmost importance to the welfare of our nation, every citizen—even a lay citizen like myself—has some responsibility to try to formulate opinions, and even express them, on the grave issues which face the medical profession.

One of the gravest of those issues and one of the most immediate, is the problem of financing medical education. The cost of medical education is constantly rising, both because of increased general costs and because constant additions to the total of medical knowledge and technic require added expensive specialization and added expensive equipment. At the same time, income on endowments to support medical education has decreased in rate, and shows no likelihood of altering its downward course. High costs and high taxes in various forms not only operate to reduce in number and amount future large, private gifts to support medical education, but also decrease the likelihood that large fortunes can be accumulated in the future, part of which would find their way to the support of medical education.

The future of medical care, including pediatric care, lies in the training of physicians to provide that care for the people of our nation. That training, in proper quality and to the necessary numbers, depends upon the prosperity and quality of American medical schools. Financially, the situation of many of those schools is perilous, and the situation of some of them is desperate.

The drastic nature of their situation has been so frequently pointed out that it should not be necessary to offer chapter and verse here. We need cite only two or three author-

ities representing various interests over the whole field of medical education. Nineteen presidents of universities with leading medical schools said in a joint statement issued in March 1947: "The present provisions for insuring a continuing supply of well-trained physicians are inadequate. They are inadequate because the medical schools which provide that supply are inadequately supported in terms of future needs. Few if any of the 70 recognized medical schools in the United States can be confident, with present resources, of maintaining in the future their program at the essential high level. Over the past 15 years private support of medical education has not been regularly maintained. Three or four medical schools came perilously near to closing during that period. Many medical schools were forced to abolish certain teaching positions; to reduce teachers' salaries and important medical services; to restrict promising research; to make very heavy demands upon the time and energy of doctors, nurses, and hospital staff; and to forego normal growth and improvement." It should be added that events since March 1947 have not only justified the above statements, but have further augmented the financial difficulties of medical education.

In fact it is no longer a question of funds to expand medical schools, but of finding funds to maintain them as going concerns. Before any expansion, must come needed financial provision to enable medical schools to maintain their present quality and numbers.

A report of the President's Scientific Research Board, headed by John Steelman, dated October 1947, states in part: "Most medical schools, especially those without state funds, are facing the prospect of reducing their training programs, or even—in a few instances —of closing altogether. Expansion is out of the question, unless substantial support is forthcoming—at a time when expansion of both (training and research) is vitally needed."

The private medical schools, which do not live on tax money, are naturally in the most difficult position. Yet their continued operation and efficiency is essential to the welfare of the nation. This is indicated by the fact that about two-thirds of the M.D. degrees conferred between 1930 and 1940 came from privately endowed institutions; that about two-thirds of the students currently enrolled in accredited medical schools are in private medical schools; and that authorities like Dr. Alan Gregg, in charge of medical sciences for the Rockefeller Foundation, estimate that some four-fifths of the significant research advances in modern times have come from graduates of private medical schools.

Where can medical schools secure the necessary funds? When one considers increased costs in nearly all fields of American life, it is not surprising that those who have studied this subject most carefully conclude that the budgets of the 77 medical and basic science schools need to be double their current total. Their current total for the academic year 1947-48 exceeds 43 million dollars. They almost certainly now need another 40 million dollars per year, and probably need considerably more than that, especially if they are to take advantage of opportunities for advancement which new discoveries have made possible.

If the needed 40 million dollars were all capitalized into endowment yielding 4% (4% is unusually high yield), the needed endowment would be one billion dollars. In terms of the possibility of securing this sum from private philanthropy alone, one billion dollars seems an impossibility. But in terms of the annual budget of the federal government, it is pin money. It is less than 1/1000 of the federal budget Mr. Truman asked

for 1948, and less than one percent of what Americans spend on recreation per year. All private medical schools would vastly prefer to operate under budgets which represented income from endowment. All private medical schools would also prefer to derive their income from sources wholly free of any danger, no matter how remote, that their programs and policies would be influenced by external forces. Ideally, therefore, they would prefer not to be dependent upon government emergency grants or subsidies. It is, therefore, the hope of most of us interested in private medical education that in the long run our medical programs can be supported largely from private sources. Careful studies indicate that there is and will be enough money in private hands in America to make full support of our present accredited private medical schools possible by private assistance alone.

But it is also obviously clear that even if funds from private resources can be ultimately secured to the adequate amount, they certainly cannot be secured in time to save some of the medical schools from closing, and most or all of them from deteriorating in quality and in morale. The only source from which funds adequate to the need can be supplied in immediately future years is obviously the federal government. Medical educators have too great an obligation to the American public to be blind, overcautious, or doctrinaire in their attitude toward the acceptance of federal funds.

From the point of view of the future welfare of medical education, it is not a question of whether or not to accept federal funds. Federal funds must be accepted—to tide over the emergency at least—and that emergency may well last five or ten years. It is a question of the terms upon which federal funds are granted and accepted, and experience does more than indicate that terms can be found upon which the federal government can provide assistance, and upon which private medical schools can accept federal assistance, without jeopardizing their freedom of action or independence in the future. The terms which the Committee for the Improvement of Child Health of the American Academy of Pediatrics recommended in their report of February 8, 1948, seem to me admirably calculated to provide federal assistance to medical schools without endangering their future independence.

In this connection I recall that when National Youth Administration funds were first made available to colleges and universities, for the support of needy students for education, many of the most conservative (and incidentally many of the best) private colleges and universities were extremely nervous about accepting those funds. Some of the leading institutions did not do so for several years, though ultimately they changed their minds. All were nervous about the regimentation or control which might result from accepting these funds. I have not in close to ten years heard any of my educational colleagues say that the acceptance of those federal funds restricted the independence of their institutions.

Before and during the war, and since, a great deal of federal money has come to universities to support research projects whether in medicine, atomic physics or other fields. If universities had refused those funds, they would certainly have greatly restricted and impaired a program of research essential to the welfare and indeed to the security of the nation. Although the acceptance of those funds in large amounts has certainly influenced the course of development of some of our educational institutions, I know of no institution which has refused large government grants, nor of any institution which feels that the acceptance of them, *upon proper terms*, has resulted in domination by federal government.

Our fears of danger are often greater in anticipation than in realization.

It behooves all educators, and particularly medical educators, to work quickly and affirmatively with state and federal government to formulate the terms by which the quality of medical education can be saved. I heartily favor the general principles of the report of Dr. Wilson's Committee, and congratulate the American Academy of Pediatrics upon its vision and promptness in preparing and pressing such a report. It would be to the advantage of medical education and future medical care if organizations representing other branches of medical service and education were equally prompt and realistic.

This brings me to some brief comments from the letter which Dr. William C. Black apparently distributed to pediatricians and other physicians under date of March 19, 1948 upon this subject.

I would not be willing to concede that Dr. Black's love for personal freedom, devotion to free American institutions, or belief in the integrity and dignity of the individual, exceeds my own. I suspect that in some circles I am myself regarded as everything from a black Republican to a Tory reactionary—those being the epithets addressed to those who have a nostalgic love for American freedom in the past, and (in my own case at least) a consuming desire that our American system can be so adapted to contemporary conditions that personal freedom, free institutions, and individual integrity and dignity can be preserved.

But I do not believe that personal freedom, free American institutions, and the integrity of the individual need necessarily be jeopardized by the acceptance of federal funds, upon such terms as those suggested by Dr. Wilson's committee, for the support of pediatric education in the near future. In fact, I have a feeling that the undernourished or crippled child, the diseased or physically handicapped man or woman, is not himself free, and has little opportunity for the utilization of freedom, for the preservation of free American institutions, or for personal dignity. In fact, if the choice were mine between the risks of federal dictatorship resulting from Dr. Wilson's program, or the risks of a future decline in pediatric education and progress through failure to adopt some program such as his, I would without question choose the former.

I do not know Dr. Black personally, so approach his letter without prejudice. I do not propose to engage in any literary exchanges with him, and this is consequently my first and last letter to you upon this subject. But I confess that I do not like the tone of his letter, which does not impress me as the scientist's calm and dispassionate pursuit of truth and reason, but the irate and prejudiced man's utilization of half-truths, emotional appeals and somewhat demagogic statements in the hope of stirring his listeners into agreement by emotional prejudice rather than by reason. If this be libelous, I hope he will not make the most of it; I am too busy and too poor to be involved in that. I do not think that the Wilson report is accurately characterized by his phrase, "fatuous platitudinous nonsense"; I do not think its philosophy (or mine) is "collectivist"; and I do not think that Dr. Wilson's program will "lead inevitably . . . to socialized medicine." I do not think the report "vicious" and I am never impressed by the term "un-American" since it means nothing unless the speaker defines precisely what he means by the appellation.

Argument by invective, and ill-tempered invective, does not seem to me to add to the wisdom of the world.

Let us be realistic. Whether or not federal support of medical education, or of higher education, is our preference, the nature of the world and its emergencies (of which this

is one) does not permit us to forego our responsibilities for the future welfare of America and the world by commanding the tide to stop rising or by thinking that we can preserve either medical education or American institutions in terms identical with 1920. A static society is a defeated society. It behooves us rather to find proper ways and means to preserve the maximum of freedom, personal integrity and human welfare. To achieve these ends I think the spirit and logic and realism of the program of the Wilson committee is more promising than the diatribes of Dr. Black.

And now, in case Dr. Black is interested, I shall pack my bag and go off to the Republican National Convention to support with enthusiasm the principles of personal freedom, free American institutions, and the integrity and dignity of the individual for which I hope that party will continue to stand.

Sincerely yours,

(signed) ALAN VALENTINE

June 28, 1948

DEAR DR. PARK:

I have read with great interest the Report of the Committee for Improvement of Child Health, "A Further Statement on Federal Aid for Pediatric Education," your "The Pediatrician and the Future" and the condemnation of the Committee's program by Dr. William C. Black.

There are four reasons why I feel compelled to write this letter. First, to point out the dangers I see in the proposed program; second, to make known to the members of the Academy certain facts, which for some reason the Committee has seen fit to withhold; third, to remove the aspersions, which intentionally or unintentionally the Committee has cast upon the Association of American Physicians and Surgeons; fourth, because I have been disturbed by the apparent blindness of the Executive Board to the probable effects of the proposed program upon the entire medical profession, a blindness which I hope does not afflict the membership of the Academy at large. I trust that the pediatricians will not consider it inappropriate for an obstetrician to present his views nor think that I am trying to dictate the policies of the American Academy of Pediatrics. Obstetricians have been working for many years in close association and usually in friendly harmony with pediatricians, while the assumption of a dictatorial attitude on my part would be presumptuous to say the least.

Those who read the transcript of the hearings on the Wagner-Murray-Dingell bill of 1946 know that ample evidence was presented to prove that the bill was written mainly by members of the Federal Security Administration. All must be aware of the fact that Arthur T. Altmeyer, Wilber Cohen, "consulting" Michael M. Davis and officials of the Children's Bureau and the Public Health Service testified in favor of the bill. Yet we find this amazing statement by the ICH Committee on page 524 of the April number of PEDIATRICS: "Any expenditure of Federal funds must necessarily be administered by a Federal Agency. Much discussion revolved about this question and many persons were consulted. It was finally agreed that neither the U. S. Children's Bureau nor the U. S. Public Health Service should be the administrating agency, but that the matter should be determined by the Federal Security Administrator *whose agency includes both the U. S. Children's Bureau and the U. S. Public Health Service.*" Why this camouflage? Why did the Committee fail to tell the medical profession its reasons for leaving out the Children's Bureau and the Public Health Service? Was it because of their past

performances? Was it because they could not be trusted? I can think of no other reasons, and I have a lurking suspicion that officials of these two bureaus were among "the many persons consulted." Furthermore, it should be apparent that they were not really excluded. *They are in the Federal Security Administration* and it is impossible for me to believe that these officials will remain quiescent while the methods of administering the program are being determined. Why, of all people, was Oscar Ewing selected by the Committee when everyone must know that he has been an advocate of state medicine for many years? Does the Committee believe that over-night the leopard will change his spots?

Another astounding thing is that by its proposal the Executive Board of the Academy has played directly into the hands of these Federal agencies, giving them far more of our liberty than they had expected. My impression has been that the proponents of state medicine had hoped first to pass the Wagner-Murray-Dingell bill and later to take over the educational programs of our medical schools. Members of the Committee may say that I am looking for a bogie man. They may quote from their statement: "It was proposed that a Council on Pediatric Education be created consisting entirely of physicians and representing both the Academy and the pediatric departments of our medical schools. The functions of this Council would be to control the allocation of grants to assure that Government funds should not bring with them dictation over the policies of the recipient institutions." This statement should be enough to convince the most skeptical that the Committee recognized the danger of a Government controlled program. In spite of this, let us see how the Committee decided that this Council was to be formed. It "should consist of nine members; should include chiefs of the Departments of Pediatrics of three approved schools of medicine; three chosen from a panel of ten nominated by the American Academy of Pediatrics; and three members who should be teachers or practitioners of medicine appointed at large. *Appointment should be by the Federal Security Administrator.*" Only three of the nine members of the Council are to be nominated by the Academy and all are to be appointed, mind you, *appointed* by the Federal Security Administrator. While I am not looking for trouble, I do not find it difficult to assume that at least six of the nine members of the Council might be quite willing to abide by the whims of the Security Administrator. The American Academy of Pediatrics is strong enough to stand alone and if it should approve the acceptance of Federal aid (which God forbid!), it should say "Mr. Ewing, here are nine names; you appoint them or the deal is off." However, no one should kid himself into believing that Washington bureaucracies give away money without expecting some kind of return, and it will take men of courage to fight for our freedom. As it has been so aptly phrased by Dr. Black, "It is safe to wager that any time the Children's Bureau propaganda experts, who are adept at reaching research conclusions to prove that a need exists for political medicine, the doctors will be out-talked, out-maneuvered, out-reported and out-recommended."

The closing paragraph in the "Further Statement on Federal Aid for Pediatric Education" is enough to overwhelm one with astonishment. I have made an honest effort to evaluate this proposal and to reach a logical, unprejudiced conclusion. To me, and I hope to many others it means just one thing, that the program is to be considered as a trial horse for complete nationalization of the medical profession. It is the invitation the bureaucrats have been patiently awaiting.

The ICH Committee has attacked the Association of American Physicians and Surgeons

by quoting a statement made by Dr. Morris Fishbein in 1946. I wonder how many members of the Committee have read the objectives of the A.A.P.S. Let me quote the first: "To organize physicians to agree to participate only in such methods of rendering medical services which are in the public interest." (Any action by the A.A.P.S. on this *is not* a proposed strike against the sick public. A.A.P.S. members will always continue to serve their patients, just as they do now and have always done in the past, but they avail themselves of their constitutional American right to refuse to do so as serfs of a political medicine bureaucracy.) Can a single member of the Committee object to this proposal? Non-participation is the means by which San Francisco physicians recently ended ten years of compulsory medical care for the city employees. In the February 28, 1948 issue of the *JAMA* there appeared an editorial entitled "British Physicians Reject Nationalized Medicine." The following is a quote from this editorial: "In a plebiscite conducted by the British Medical Association 86% of British physicians voted against working for the universal free medical scheme that has been scheduled to take effect July 5. The British physicians are not striking against the sick; they will care for their patients but will not accept payment from the government." The editorial must have been written or endorsed by Dr. Fishbein and is exactly what the A.A.P.S. has proposed for several years. In a letter to me dated May 15, 1948 Dr. Fishbein wrote as follows: "The Board of Trustees of the American Medical Association and the House of Delegates have given their approval in principle to all organizations which oppose state medicine and compulsory sickness insurance." Continuing its attack the Committee said "It is apparent that many have confused this organization (A.A.P.S.) with the National Physicians Committee whose efforts have been repeatedly endorsed by the House of Delegates of the American Medical Association." Under the date of June 25, 1948 M. S. Petersen, Associate Administrator of the National Physicians Committee wrote to me as follows: "We are delighted that the A.A.P.S. is in the fight. The threat of non-compliance is undoubtedly effective. Actually, however, recent developments in Britain indicate that a large percentage of the medical profession has decided to go along with the government, in spite of the fact that they once voted not to." Not only does this letter refute the innuendoes of the Committee, but it brings out into the open the most serious threat to our independence; namely, the lethargy, procrastination and wishful thinking of too many of our profession here in America. Let us hope and pray that we will not make the mistake of our British friends. Let us not wait until state medicine is forced upon us. If we have the courage and will to act promptly, we can shape our own destiny. It might interest your readers to know that in addition to many county societies fourteen state medical societies have now endorsed the Association of American Physicians and Surgeons.

At the annual meeting of the New York State Medical Society held in May, 1948 an effort was made to secure the Society's endorsement of the Committee's program. I am happy to report that the House of Delegates sensed the hidden dangers of the proposal and refused endorsement.

While I do not question the need of money by pediatrics and every other branch of medicine, I am not willing to see our honorable profession sell its birthright for a mess of pottage. I urge those who may read my letter to stop, look and listen before they agree to cooperate with Washington bureaucracies which are using the back door to gain partial control of our educational system. Every one of us should ask and answer this question, "CAN WE AFFORD TO TAKE THE CHANCE?"

Yours sincerely,

(signed) THOMAS O. GAMBLE

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*
Philadelphia, Pa.

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

TWO months ago when some of the salient features of the National Health Assembly were reviewed in this column (July issue), the report of the Maternal and Child Health Section was reserved for more complete presentation. This Section report is far too bulky to be quoted fully here. It includes first a factual summary of the present status of maternal and child health under the heading: "Where are we now in Maternal and Child Health?" Sub-committees, each of which submitted separate reports, were appointed to consider the following topics:

1. Training of personnel
2. Health of the School Age Child
3. Parent Education
4. Program to Raise Standards of Maternity, Newborn, and Pediatric Hospital Care
5. Research Program in Child Life
6. Care of the Handicapped, Including Prevention of Accidents

Because other sections of the Assembly considered nutrition, dental care, environmental sanitation, mental hygiene and the chronic diseases common in childhood, these important factors were not considered in detail by the Maternal and Child Health Section.

The most important part of the report is a summary entitled: "Goals for Maternal and Child Health." This statement includes the Sub-committee recommendations which were agreed upon as the most significant. This summary is therefore quoted in full as follows:

GOALS FOR MATERNAL AND CHILD HEALTH

Whenever stock is taken of achievements designed to increase the chances of a good life and to improve the conditions of living, the people turn to examine the status of public and private action in behalf of children and to assess the extent and quality of care provided. This is natural because we recognize that the good life for mankind and world peace lies in the health and vigor of children, in their capacity to learn, in their ability to grow as thinking, reasoning human beings, and to develop from infancy through childhood and youth until they reach adulthood as fully mature persons, secure in their ability to take their places as citizens and as parents.

The overall goal toward which we are working is to assure every child the experiences in life that will result in his attaining adulthood, fully mature and healthy in body and mind, emotionally secure, able to give more than is asked for, to face success and frustration with equanimity, to be self-reliant, to cooperate with his fellows, to take his place in a democratic society as a thoughtful, responsible citizen concerned with the common good, and "to live harmoniously in a total changing environment."

At this time our task is to point out gaps in the services and programs and to lay down broad lines of advance during the next ten years that will help children along the road to that healthful life, as described by the World Health Organization as "a state of complete physical, mental and social well-being," and not merely the absence of disease.

This is not a job to be completed by us in our lifetime, but many of the goals set forth below could be attained rapidly if vigorous action were taken. We have the technical knowledge and skills to attain them, but this knowledge is not being put to work because certain economic, sociologic or psychologic barriers block the path. These barriers must be destroyed as rapidly as we discover the methods for destroying them. Fortunately we already have soon tools to begin our task.

Certain phases of the total program of maternal and child health stand out as most in need of concentrated attack in the immediate future in order to make substantial progress toward all goals within the next ten years. This should not be interpreted, however, as meaning that action toward all goals outlined by the subcommittees must not go forward simultaneously.

Recommendations

1. A vigorous program of research in matters related to child life should be established and supported where necessary by increased Federal grants. Such research should include a combined attack from fields of medicine, psychology, anthropology, sociology, education, economics and other related fields, with special emphasis on accidents, rheumatic fever, premature birth, child behavior, the ways of modifying attitudes of parents, and the effects on children of the changing patterns of family life.

2. A central clearing house should be established in which research problems and projects may be recorded in order to maintain a free exchange of information for all workers, to avoid duplication of effort, and suggest research needed to fill gaps in our knowledge.

3. Federal grants should be increased and extended to provide training of professional personnel responsible for medical care and health supervision of mothers and children.

4. The newer knowledge in child rearing, in pediatrics, obstetrics and related fields must be brought to those on the job of caring for mothers and children through extension courses and other methods, particularly to the general practitioner.

5. The Children's Bureau with other appropriate Federal agencies and professional organizations should develop standards of care for maternal and child health. The psychologic, social and physical needs of the individual should be taken into account. Standards should be set up whenever possible in a form that makes them useful to the local community that wishes to use them.

6. There should be only one standard of hospital care for all mothers and children—that which puts into practice the newest and best medical and nursing knowledge and technics for each patient and uses every modern facility and service, on the basis of medical need, rather than on the basis of ability to pay or other barriers. This care must insure the emotional security as well as the personal dignity of each patient and family.

The development or revision of hospital licensing systems is recommended. Systems which provide merely inspections for sanitary and dire hazards and emphasize minimum standards are inadequate. A revised licensing system, placing full authority in the hands of the health department, should aim at achieving standards, not minimum requirements. The enforcement of licensing laws is more effective in raising the level of service in

hospitals when, rather than mere inspection, educational guidance is provided by highly qualified hospital consultants.

7. A positive program of mental health should permeate all services for mothers and children, and be an integral part of all community health programs for children, including those for adolescents.

8. A vigorous program for education of parents in child rearing should be undertaken. Although members of many professions and a variety of community agencies are concerned with this program, the prime responsibility must rest with health and education authorities who should develop and maintain extended programs for parent education.

9. In the education of physicians, nurses, social workers, teachers and other professional personnel who work with children more information concerning growth, development and behavior of normal children should be included.

10. A comprehensive program of nutrition service and nutrition education should be an essential part of all health, education and welfare programs for mothers and children. An adequate number of qualified nutritionists should be provided for this purpose.

11. That local communities should take initiative in developing experimental projects designed to solve their own local problems and that a wide variety of methods of attack should be encouraged.

12. Since accidents are the chief cause of death of children above the age of one, it is recommended that accident prevention be considered a major responsibility of State and local health departments and that persons qualified in this field should be included on their staffs.

13. To have an adequate and sound national plan for the treatment, care and rehabilitation of children with physical and mental handicaps, a census of such children should be taken by the Federal government at regular intervals beginning with the census in 1950.

14. Services for rehabilitation of physically and mentally handicapped children should be expanded with increased Federal and State support and coordinated with programs of voluntary agencies. Current planning for the relation of medical centers to regional and community hospitals should be considered in connection with the development of more and better institutional, out-patient and convalescent service and after-care of handicapped children.

15. Because of conflicting and restrictive laws and regulations children are often prevented from securing available health services. A critical study should be made which should result in the removal of such legal limitations and promote better care.

16. The Federal Security Administrator should call a national conference on school health with adequate representation of the constituent units of the Federal government and of medical, public health, dental, nursing, educational, and other professional and related voluntary and lay groups to determine goals and recommend procedures for the following purposes:

a. To clarify the contributions which all related groups can make and determine how they can best work together.
b. To help insure more systematic, better coordinated and widespread programs.
c. To promote integration of school efforts with those in the community; and
d. To set an example of coordinated action for States and for local communities.

The Governors of the respective States and appropriate local officials should be encouraged to call similar State, county and city-wide conferences.

17. Federal and State aid should be provided for the extension and improvement of an integrated program of health instruction. Physical education and health services are indispensable and inherently related parts of an effective program for all children of school age.

18. Advances made in past years toward developing and reaching optimum standards and practices of employment and working conditions of women and minors are of vital importance to the health of our Nation's children. Legislation and practices in this regard should be strengthened rather than being permitted to go backward as was threatened in many parts of the country and occurred in some during the stress of the war and postwar periods.

19. To achieve complete health for every child, voluntary and official agencies should develop closer working relations and seek every opportunity for joint effort.

NEWS AND ANNOUNCEMENTS

The Heart Division of the San Francisco Tuberculosis Association announces the Nineteenth Annual Postgraduate Symposium on Heart Disease to be held October 27-30, 1948, at the St. Francis Hotel. The symposium is sponsored by the Academy of Pediatrics, Northern California. For hotel reservations or further information write the Heart Division Office, 604 Mission St., San Francisco 5, Calif.

The American College of Physicians will conduct its Thirtieth Annual Session at New York City, March 28 to April 1, 1949. The College further announces that a limited number of Fellowships in Medicine will be available from July 1, 1949 to June 30, 1950. They are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation; and are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2,000 to $3,200. Application forms on request: 4200 Pine St. Philadelphia 4, Pa., by no later than November 1, 1948.

* * *

A reduction in the number of child accidents, is the objective of an intensive child safety campaign launched this fall by the Metropolitan Life Insurance Company with the cooperation of the Academy, the Children's Bureau, and the National Safety Council.

Accidents are the leading cause of death among children of more than one year of age. The present relatively low death rates from all non-accident causes, as compared with those of but a few years ago, are the result of advances in medical science and concentrated efforts in the field of child health. Efforts must now be intensified to bring about a reduction on the number of child accidents as well. The program is planned to encourage public health, medical, safety, and other organizations, as well as the general public, to give even greater attention to the child safety phase of the child health program.

As part of the campaign the Metropolitan has prepared a 12-page, illustrated booklet, "Help Your Child to Safety," which stresses the importance of cooperation on the part of all members of the family for child safety, and emphasizes ways to combat physical hazards and unsafe practices resulting in child injuries.

Supplies of the booklet, copies of statistical charts, prepared talks, and other source material are available for use in local organized child safety programs.

* * *

Dr. Henry G. Poncher was named by the senior students at the University of Illinois College of Medicine as a winner of the Raymond B. Allen Instructorship Award, designed to honor excellency in individual instructorship rendered by faculty members to students. Dr. Poncher, head of the Department of Pediatrics, was honored for clinical instruction.

* * *

Dr. John P. Hubbard, of Washington, D.C., has been appointed assistant professor of pediatrics at the University of Pennsylvania School of Medicine. He will simultaneously conduct a rheumatic fever teaching program throughout Pennsylvania under the auspices of the State Health Department. Dr. Hubbard will continue to direct the Academy's Improvement of Child Health program from its new offices at the Children's Hospital, 18th and Bainbridge Sts., Philadelphia, Pa.

* * *

The Distinguished Service Medal of the American Medical Association recently was awarded by the House of Delegates to Dr. Isaac A. Abt of Chicago. Dr. Abt was the first president of the American Academy of Pediatrics in 1930.

Deaths: News has been received of the recent deaths of two Academy members: Dr. John Aikman, Rochester, N.Y., authority on accidental poisoning in children, died July 13. Dr. Oscar Reiss, Beverly Hills, Calif., died June 16 of coronary thrombosis. Dr. Reiss was serving as Chairman of the Section on Pediatrics of the A.M.A.

* * *

The following candidates were certified by the American Board of Pediatrics following examinations in Chicago on June 26 and 27. A total of 2822 pediatricians have now been certified.

John H. Cordes, Jr., M.D., 216 Empire Bldg., 302 Central Ave., St. Petersburg, Fla.
Victor J. Cordes, M.D., 7405 Harwood Ave., Wauwatosa 13, Wis.
Susan Coons Dees, M.D., Duke Hospital, Durham, N.C.
Harold X. Gerber, M.D., 1046 Wilson Ave., Chicago 40, Ill.
John Roland Harvin, M.D., 206 N. Sumter Ave., Sumter, S.C.
Maurice Kaufmann, M.D., 2 Nassau Place, Hemstead, N.Y.
John T. Kometani, M. D., 1430 Tulane Ave., New Orleans, La.
William Caldwell Layton, M.D., 2300 Ralston Ave., Burlingame, Calif.
Jacob S. Light, M.D., 405 37th Place, S.E., Washington 19, D.C.
Bernard L. Lipman, M.D., Medical Arts Building, Philadelphia, Pa.
Dan Campbell McDougall, M.D., 210 Kane Building, Pocatello, Idaho
Irving Howard Mauss, M.D., 443 Beach-138th St., Belle Harbor, N.Y.
Evelyn E. Miller, M.D., 1642 Harrison St., Philadelphia 24, Pa.
Dominic S. Motsay, M.D., 111 W. Lockhart St., Sayre, Pa.
Brian St. John Moynahan, M.D., 334 Washington Ave., Belleville, N.J.
Harry Thomas Nagel, M.D., 518 S. 5th Ave., Maywood, Ill.
Louis J. Needels, M.D., 402 Loma Alta Drive, Santa Barbara, Calif.
Phyllis T. Mrazek Orland, M.D., 6628 W. Cormak Road, Berwyn, Ill.
Herbert J. Palmer, M.D., 170 E. 77th St., New York, N.Y.
John Lyman Peck, M.D., Johns Hopkins Hospital, Baltimore 5, Md.
Walter Pick, M.D., 42 Fox St., Fitchburg, Mass.
Bernard C. Prietsch, M.D., 4752 Baldwin Manor Road, Pittsburgh, Pa.
Francis Lupton Robinson, M.D., 280 MacArthur Blvd., West, Oakland, Calif.
Joseph L. Rubel, M.D., 5 E. Gregory, Pensacola, Fla.
Henrietta K. Sachs, M.D., 1820 Juneway Terrace, Chicago 26, Ill.
Joe M. Standefer, M.D., 934 42nd St., Des Moines, Iowa
Meritt W. Stark, M.D., Child Research Council, 4200 E. 9th Ave., Denver, Colo.
Walter Milton Tasem, M.D., 619 S. Bonne Brae, Los Angeles, Calif.
Herbert Allan Wenner, M.D., University of Kansas Hospital, Kansas City, Kan.
Norman C. Woody, Jr., M.D., 1430 Tulane Ave., New Orleans 13, La.
Charles Richard Yoder, M.D., 705½ E. Walnut St., Bloomington, Ill.

The following men were certified in the Sub-Specialty of Allergy on June 25, 1948 by the American Board of Pediatrics in cooperation with the Committee on Allergy of the American Board of Internal Medicine:

Gerald M. Cline, M.D., 620 Greisheim Bldg., Bloomington, Ill.
Norman W. Clein, M.D., 1155 10th Ave., North, Seattle 2, Wash.
Susan Coons Dees, M.D., Duke Hospital, Durham, N.C.
Salmon Reclus Halpern, M.D., 3520 Fairmount, Dallas, Tex.
William Allen Howard, M.D., 1517 30th St., N.W., Washington 7, D.C.
Edward Scott O'Keefe, M.D., 31 Broad St., Lynn, Mass.
Charles H. Pettet, M.D., 2200 W. 3rd St., Los Angeles 5, Calif.
Robert H. Trimby, M.D., 122 W. Hillsdale, Lansing, Mich.

INTERNATIONAL NEWS AND REPORTS

Special volumes of Acta Paediatrica will appear in the near future: (1) The Transactions of the Fifth International Pediatric Congress, New York, July 1947 (Vol. XXXVI of Acta Paediatrica). Price 25 Swedish crowns. (2) General Index. (Vol. I-XXX) Price 15 Swedish crowns.

Orders should be sent to: Acta Paediatrica, Polhemsgatan 30, Stockholm, Sweden.

* * *

Dr. Martha M. Eliot, Associate Chief of the Children's Bureau, is one of the three official delegates appointed by the President to represent the United States in the World Health Organization, meeting in Geneva, Switzerland.

* * *

The Canadian Society for the Study of Diseases of Children announces the election of the following officers for 1948-49: President, P. E. Williams; Vice-President, H. I. Palmer; Sec'y-Treas., R. L. Denton; Senior Councillor, F. W. Jeffrey; Junior Councillors, J. D. Keith and Jessie Boyd Scriver; Western Division; D. B. Leitch; Eastern Division, F. W. Tidmarsh.

The following new members have been admitted to the society: Regular members—Euclide Dechene, Donat Lapointe, R. H. McCreary, Maurice D. Young, and John Fletcher. Associate members—Eleanor Harpur, A. L. Johnson and Donald L. McRae.

The society's 1949 Annual Meeting is scheduled for on or about June 18 at The Thousand Islands Club, Alexandria Bay, N.Y.

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

116TH ANNUAL MEETING OF THE BRITISH MEDICAL ASSOCIATION AT CAMBRIDGE, June 25 to July 2, 1948

SECTION OF CHILD HEALTH

The subject of the discussion on Thursday morning July 1 was "Neonatal Mortality and Morbidity." With the president Sir Leonard Parsons in the chair, Dr. Agnes R. MacGregor (Edinburgh) opened the proceedings by giving a pathological survey.

She stressed the importance of cooperation between clinician and pathologist to improve certification of death and thus the accuracy of statistics. Unfortunately most records are from maternity hospitals which are not entirely representative of the whole community. Intracranial haemorrhage and infection caused the highest number of deaths in the neonatal period, but there had been a considerable rise of developmental defects as a cause in premature infants. Dr. MacGregor considered that an infant can survive a mild intracranial haemorrhage at birth but that haemorrhage is not necessarily present in all babies showing cerebral irritation, which may be caused by oedema of the brain. She concluded that infection was the overwhelming cause in her series of deaths after the seventh day of life.

Professor L. S. Penrose (London) then discussed some congenital abnormalities and genetic factors contributing to neonatal mortality and morbidity. The factors influencing the production of congenital defects he divided into two groups: environmental, and genetic. Not uncommonly however it was the effect of a combination of the two. The neurologic abnormalities such as hydrocephalus, spina bifida, anencephaly and mongolism composed the largest groups of defects. Professor Penrose showed that congenital malformations predisposed to stillbirths and neonatal deaths but during the usual period of fertility the incidence of congenital malformations was minimal. If conceptions were limited to the optimum maternal age period, the number of congenital abnormalities and therefore stillbirths and neonatal deaths might be reduced.

Dr. Winifred Young (Birmingham) then described some physiological handicaps in premature infants. After enumerating the causes for increased susceptibility to infection in premature infants she showed that 4 grammes of protein per kilogram of body weight a day were required in order to maintain the same retention of proteins as would have occurred in the foetus in utero. Dr.

Young showed charts demonstrating the increased gain in weight when more proteins and calories were given, and the inadequate gain when a low protein intake was given. She showed that inadequate development affects the infant's resistance to infection leading to an increased mortality rate.

Professor N. B. Capon (Liverpool) discussed some of the obstetrical factors contributing to neonatal mortality. Referring to physical trauma during birth he considered the critical period for the infant was when the membranes ruptured. Describing the dangers in placenta praevia he said the infant mortality was seldom less than 20%, often as high as 50% but this was already showing an improvement since the introduction of more caesarean sections for prolongation of labour in spite of placenta praevia, for this condition. Professor Capon then enumerated the dangers to the infant from the use of anaesthesia and drugs to the mother during labour recommending that only the least harmful of these drugs should be used.

Dr. J. L. Henderson (Edinburgh) spoke on infections of the new-born. They caused more deaths after the first week of life than all the other causes put together. He mentioned the importance of the staphylococcus in conjunctivitis and skin infections and considered that nurses hands were the most important infecting link between the babies. He concluded by recommending general measures to reduce infection.

In the afternoon of July 1 the nutritional experiments that had been in progress in Germany over the last two years under the direction of Professor R. A. McCance (Cambridge) were described. Dr. Elsie M. Widdowson (Cambridge) demonstrated the effects of giving the meagre German rations plus as much bread as they wished for and added vitamins to girls and boys in a German orphanage over a period of a year. They put on twice as much weight and 1½ times as much height as was to be expected for their age. Five children were shown, all of whom looked healthy and strong.

Dr. R. F. A. Dean (Cambridge) reported that at the end of a year the children's energy had increased and their posture and muscular development had improved, abdominal distension soon disappeared, their contours became less angulated although there was no excess of fat. Skin sepsis was less but they still looked pale. It was noted that the thyroid gland enlarged in a number of the girls.

In the discussion that followed it was agreed that following starvation weight gain is greater than for a well nourished person.

On Friday, July 3, malignant disease in infancy and childhood was discussed. The opening speaker Professor Wilfrid F. Gaisford (Manchester) explained that although there was nothing to suggest an actual increase in incidence of malignant disease, its importance as a cause of death showed a relative increase since the control of other diseases by chemotherapy. He took an optimistic outlook on prognosis, although the mortality was high particularly in the first five years of life. Many cases of cure had been reported following surgery or radiotherapy.

Dr. C. G. Teall (Birmingham) spoke on the radiological diagnosis of malignant disease. He explained the limitations in this field of work unless closely combined with clinical findings. In kidney tumours a pyelogram was of more help in demonstrationg a normal kidney on the opposite side than in helping to differentiate the type of tumour on the diseased side. Dr. Teall demonstrated the difficulty in differentiating bone tumours by X-ray and recommended confirmation by biopsy.

Professor J. S. Mitchell (Cambridge) discussed the radiotherapy of malignant disease. He explained its limitations as a result of a toxic heparin-like substance that was liberated as well as the late effects on the vascular system and other organs in the vicinity of radiation, particularly the endocrine glands and lens of the eye. He did not consider radioactive isotopes should be used in children on any non-malignant condition because of the danger of long term deleterious effects.

Dr. A. M. Barrett (Cambridge) discussing the pathology of malignant disease, differentiated the true embryonic type of tumour which mostly occurred in the young age group with tumours occurring at any age. When multiple tumours were present in the embryonic type a multicentric origin should be considered rather than the possibility of secondaries.

In the afternoon Dr. Janet D. Roscoe (Cambridge) demonstrated at the County Maternity Unit work in progress on the weights of normal neonates. She had compared the weights of 130 newborn children given breast feeding only with 203 which had been complemented in the first three days. Although there was a greater loss of weight in the first two or three days in the breast fed by the ninth day they had reached the same weight as the complemented babies. Dehydration fever was more common in those not complemented but was easily corrected by giving water. A lively discussion followed.

C. Elaine Field, M.D.

BOOK REVIEWS

SKELETAL TUBERCULOSIS, Vincente Sanchis-Olmos. $5, 246 pages, 104 illustrations, with numerous diagrams. Williams and Wilkins Co., Baltimore, 1948.

This latest publication gives the English language audience the benefit of the author's many years of interest in orthopedic problems, and especially those of children. The text has been translated from Spanish by Dr. John G. Kuhns, with a foreword by Dr. Frank R. Ober, both of Boston, where the author completed preparation of the text.

Part I of the book very adequately presents current concepts of pathogenesis, etiology, allergic phenomena, pathology, and clinical types of skeletal tuberculosis. Constant awareness of the total systemic process is emphasized. Excellent chapters are included on differential diagnosis, auxiliary diagnostic procedures, and prognosis.

Part II deals with the problems encountered with the specific skeletal lesions, reviewing pertinent portions of Part I for each lesion, and giving an extensive discussion of therapy, omitting specific orthopedic details. The book gives one a working concept of skeletal tuberculosis, a familiarity with the current trends both here and abroad, and a clear picture of the problem in relation to pediatric practice.

DOUGLAS T. LINDSAY

PROCEEDINGS OF CONFERENCE ON METHODS FOR EVALUATING NUTRITIONAL STATUS OF MOTHERS, INFANTS AND CHILDREN, 93 pages, *The Children's Fund of Michigan,* Detroit, Mich, 1947.

The comments of Dr. Icie Macy Hoobler, Chairman, and 22 guest conferees, well qualified to discuss this subject, are reported in the Conference Proceedings. The first half of this Report is devoted to problems relating to the determination of food intakes and the conversion of items of foods into specific nutrients.

The diet history is contrasted with a food intake record, the former being an attempt to find an "average" intake drawn from a long period of time, while the latter aims at recording accurately what was eaten during a short but specific period. Either a three or a seven day period is usually chosen for the food intake record. It is stressed that the diet history should be taken by an experienced interviewer who has the ability to obtain the desired information regarding the patient's food habits. Specimen diet record and diet history forms are included with instructions regarding their use. Two shortened methods for calculation of diets are also discussed but the limitations of these procedures are pointed out.

Several conferees stressed the importance of refraining from using data collected in this way for research or other purposes which require greater accuracy than they provide. The pediatrician who is interested in conducting research which may involve the food consumed by his patients would find it useful to study the methods of evaluation of diets reviewed.

The next section of the Report deals principally with blood determinations and the problems of measuring and interpreting blood levels. A discussion regarding the use of the Lowry and Bessey microtechnics led to some interesting remarks on hemoglobin levels and serum alkaline phosphatase; both these determinations show age and sex differences. Although there is wide variation between individuals, it is reported that the serum phosphatase level of a given person is very constant, provided corrections for age are made. An elevated phosphatase is found in conditions in which there is high osteogenic activity but lack of calcification with a resulting layer of uncalcified osteoid tissue. These include Paget's disease, rickets and conditions associated with rapid growth of bone.

Many of the problems raised at the Conference are the concern of the worker engaged in fundamental nutrition research but references to the studies on human milk would stimulate those interested in infant feeding to review the results of work that has already been published and to look forward with interest to further research from the laboratory of the Children's Fund of Michigan.

The amount of money available for food is often the limiting factor in the mother's ability to follow a doctor's advice in feeding her children: the low-cost adequate diets with sample menus

and some reference to low-cost foods should be helpful to the pediatrician who is prescribing for patients of low income.

HAROLD C. STUART

AMERICAN CHILDREN THROUGH THEIR BOOKS, 1700-1835. Monica Kiefer. Foreword by Dorothy Canfield Fisher. $3.50, illustrated, 248 pages. University of Pennsylvania Press, Philadelphia, Pa., 1948.

This is not only a book about children's books, but it is also a comprehensive survey of various aspects of child life in America during the colonial and early national periods. Miss Kiefer's major conclusion is that the American Revolution marked the beginning of the American child's emancipation, and that by 1835 one finds the child emerging as a distinct personality not only in respect to religion but also in education, manners, health and recreation. The chapter on "War with the Devil," in which is discussed the gruesome theology of early New England and its effect on all phases of child behavior, is skillfully handled with both respect and delicate irony. That even some infants were born totally depraved and predestined to eternal damnation was indeed a frightening thought, but to be transported directly from New England, "this Land of Light to that Dungeon of Eternal Darkness," should have been enough to transfix any good old Puritan on the spot. But did not the constant repetition of these threats of everlasting torture mean that many children totally disregarded them, just as many of them do now? One recalls the mortification of the strict, stern, humorless Reverend Ebenezer Parkman when he discovered his own children reading the *Life of Patty Saunders,* with its "Amour & Intrigue . . . cloth'd in ye ensnaring Language of the Age"; and also the truly sensational uproar of 1744 which resulted when the godly junior Puritans of Northampton, Mass., were caught surreptitiously circulating the latest textbook on obstetrics.

Pediatric psychiatrists will find many interesting items in the chapter on "decent behavior" of children in the meeting-house, at home, at meals, and particularly among their elders. Parents were instructed to:

"Break their wills betimes. Begin this work before they can run alone, before they can speak plainly, or speak at all. Whatever pain it cost, conquer their stubborness; break their wills if you would not damn the child."

Educators will undoubtedly profit from the account of the early hornbooks, primers, spellers, and geographies; and the gradual evolution in methods of teaching the young. Learning the alphabet from:

"In Adam's Fall, We sinned all.
Thy Life to men, This Book attend."

was changed in subsequent editions of the primer to:

"A was an Angler, and fished with a hook.
B was a Blockhead, and ne'er learn'd his book."

The evolution of illustrated books is also interestingly told.

The chapter on medical care of children unfortunately cannot be called a valuable contribution to the history of American pediatrics, for although it holds the reader's interest, it is too much concerned with the old remedies which now appear ridiculous, but which were certainly not ridiculous when parents frantically grasped at any straw that might help a dying child. This reviewer also wishes that Miss Kiefer had omitted so many quotations from foreign authors, and particularly from James Nelson, who, overshadowed by the illustrious William Cadogen, apparently did not have much influence even in his own little neighborhood of Red Lion Square in London. For Walter Harris, who belongs to seventeenth century London, could have more profitably substituted one of the best of early American pediatricians, Lionel Chalmers of Charleston, S.C. Since sickness, however, was a very important, if not the most important aspect of child life in early America, this chapter is necessary to complete the story.

The book is well organized, charmingly written, and shows considerable evidence of originality. The illustrations are choice and delightful. Miss Kiefer has rendered a valuable service in calling attention to many sources of information that have hitherto been too much neglected by authors concerned with child life in the early days of this country. The book can be heartily recommended.

ERNEST CAULFIELD

EDITORIAL

CHILD ACCIDENT REDUCTION: A CHALLENGE TO THE PEDIATRICIAN

THE application of the principles of preventive medicine to children has brought about almost unbelievable improvement in mortality from the so-called common childhood diseases. In fact, the control today over smallpox, diphtheria, the diarrheal diseases, pneumonia, and others, has brought pediatrics face to face with the present leading cause of childhood mortality—accidents. Accidents not only kill more children after infancy than does any single disease but also, in the ages from one to 14 inclusive, accidents take as many lives as pneumonia, diarrhea and enteritis, measles, diphtheria, meningitis, poliomyelitis, whooping cough, and scarlet fever combined.

This month the Academy, in cooperation with the U. S. Children's Bureau, the National Safety Council, and the Metropolitan Life Insurance Company, is beginning a sustained national effort to reduce accidents to young children. A statement describing the insurance company's part in the initial phases of this program appears in "News and Announcements" this issue. The National Safety Council, through its monthly "Operation Safety" program, will focus attention during September on the child, especially at the school ages; the Children's Bureau is publicizing this program through its publications and regional medical directors. Academy members will shortly receive a letter from Dr. Albert D. Kaiser, our representative on the committee of the sponsoring agencies, which will describe the campaign and send copies of the educational material prepared for this purpose.

It is time we turned our attention to this formidable enemy of child health. As physicians, we should adopt a more critical attitude toward the cause of accidents. We should approach accidents with the same inquiring mind that we bring to the study of disease. We tend to forget that not so long ago accidents and disease were linked together as due to "bad luck" or evil spirits. Interestingly enough, the first scientific studies in the causation and prevention of accidents were made among adults. It has long been recognized that some individuals appear more susceptible to accidents than others.[1] We are only beginning to study accidents in children from this point of view, where accident proneness of emotional or physical origin is by no means negligible. A clinic has been opened at the Municipal Hospital in Rochester, N.Y., sponsored by the University of Rochester Medical School and the Rochester Health Bureau to study accident-prone children and their families. Children who have reported repeatedly in the emergency department for some accident are being thoroughly studied from a physical and psychologic standpoint. With the assistance of a public health nurse, the home environment is investigated. An attempt is being made to determine the cause of repeated accidents in these children.

The importance of attention to accidents is seen in Werne and Garrow's[2] recent report on postmortem studies of infants who died of suffocation. They offer evidence to show that some deaths commonly certified as due to accidental mechanical suffocation resulted from other causes, in many cases, from respiratory infections. Press has given some valuable suggestions to physicians on the handling of the accident problem.[3]

It is in the runabout period, one to five years, where the least improvement in accident mortality has occurred. This is the period when the pediatrician should intensify his safety education of the parents. At this period, parental supervision begins to relax. Because parents are often overly anxious about their children during infancy, the pediatrician may feel it necessary during that period to allay many of their unwarranted apprehensions. But when the child begins to toddle about, to investigate, to test his muscular skill, the pediatrician should point out to parents that opportunities for exposure to accidental injury, such as burns, scalds, falls, and poisoning, increase as the range of the child's activities widens. It is appropriate to begin this educational program as soon as the child begins to creep and explore, and to attempt to anticipate with the child's parents some of the accident situations which might arise. Handled in this way, it will seem to the parents a natural part of the child-rearing program and will not be likely to produce in them attitudes of anxiety, fear, and over-protection. The "dose" and the "technic" of safety education is a matter of professional judgment. The child's personality, his muscular coordination, his physical environment and the parents' emotional attitude toward the child and the doctor, are factors which determine *what, when,* and *how much* should be discussed.

Two factors characteristic of child development are frequently at the root of accidents—the desire of children to imitate others, especially their parents, and their fondness for repetition. If the parent is heedless in his actions, the child may follow suit. If the child does a hazardous thing and avoids disaster, he is likely to repeat the procedure. An illustration of this tendency to repetition was seen recently when a two-year-old was killed in a fall from a second story balcony. The father said the child had been observed repeatedly climbing out of his crib, pushing a chair over to the balcony railing, and climbing up—yet nothing had been done to prevent what any person with knowledge of child behavior could have predicted would end tragically.

The prevention of child accidents is a formidable challenge to pediatricians. One group of New York physicians which has already taken constructive action is the Child Welfare Committee of the New York County Medical Society, under the direction of Dr. Alfred E. Fischer. As community leaders, pediatricians can make a further contribution to the reduction of child accidents by presenting the facts to their medical colleagues in general practice; and by assisting health departments and voluntary agencies, such as parent-teacher associations to develop community educational programs. Through their knowledge of child behavior and growth, pediatricians can contribute to improved understanding of accident-prone children.

GEORGE M. WHEATLEY, M.D.

REFERENCES

1. Dunbar, Flanders, Mind and Body: Psychomatic Medicine, Random House, 1947.
2. Werne, J., and Garrow, Irene, Sudden deaths of infants allegedly due to mechanical suffocation, Am. J. Pub. Health 37:675, 1947.
3. Press, E., The Accident Problem, J.A.M.A. 135:824, 1947.